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## Oral and Cranial Implants

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Editors

# Oral and Cranial Implants

Recent Research Developments

*Editors*

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## Preface

We have tried to provide an evidence-base to some of the most important concepts in implantology. It will also provide a readable information source for the practitioner as well as a heavily referenced text for the researcher and specialist. We ask for feedback from our colleagues, students and manufacturers to help us improve future editions, as we regard this as a work in progress.

Hugh Rodman Leavell and E. Gurney Clark proposed the three-stage concept of preventive medicine: Primary Prevention for promotion of general health; Secondary Prevention for early diagnosis, prompt treatment and disability limitation; and Tertiary Prevention for rehabilitation.<sup>1</sup> Dental caries, periodontitis or injury in the oral cavity may be addressed by primary and secondary preventive measures. However, once the affected teeth are removed, there are new challenges in rehabilitation of the edentulous jaw. The goal of tertiary prevention is to maintain the biopsychosocial health of individuals, which is defined by the World Health Organization as “a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity.”<sup>2</sup>

Contemporary dental implants have achieved a high success rate as measured by initial osseointegration. However, the treatment effectiveness of implant dentistry should be further defined from the successful attainment of the long-term stability of oral and general biopsychosocial health.

Each of the authors is involved in implantology research and scholarship and has provided their insights and experience to the book. Wherever possible, we have used experimental evidence to recommend the best methods of obtaining and maintaining osseointegration, but there is much controversy surrounding some issues. Obtaining even a consensus on some basic issues, such as the definition of peri-implantitis, has triggered much discussion amongst the authors.

It is well known that implants are a generally successful form of treatment, but we set out to explain how implants fail due to infection, mechanical loading and biological and genetic issues. The result of implant failure for the patient may have serious consequences, especially for those with craniofacial

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<sup>1</sup> Leavell HR, Clark EG (1965) Preventive medicine for the doctor in his community: an epidemiological approach. McGraw-Hill Book Co., New York.

<sup>2</sup> Grad FP (2002) The preamble of the constitution of the World Health Organization. Bull World Health Organ 80(12):981–984. [www.who.int/bulletin/archives/80\(12\)981.pdf](http://www.who.int/bulletin/archives/80(12)981.pdf)

and maxillofacial implants. Unfortunately, implant failure is more frequent in these patients.

Finally, we wish to thank those colleagues who have provided us with constructive criticism and inspiration and our patients who inspire us each day to do what we do.

Manchester, UK  
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## 1.1 Introduction: “Peri-implantitis” and “Osseoseparation”

Success of osseointegrated dental implants has been consistently high in most clinical situations where proper diagnostic procedures, treatment planning, and surgical placement have taken place. Osseointegration is the intimate contact of a titanium implant with a bone surface. There is no reported chemical bond taking place between bone and titanium, but there is an absence of fibrous scar tissue. It has been believed that once osseointegration is established between bone and implant surface, this intimate relationship continues to be maintained. The sustained osseointegration has provided the biological rationale for favourable long-term prognosis of dental implant therapy. However, with the increasing use of dental implants placed in ever more demanding circumstances, the number of complications has also risen.

Peri-implant diseases are one of the most common biological complications. The histological reaction of the tissues surrounding an implant to plaque is similar to that of the natural tooth (Sanz et al. 1991). Clinical presentations highlight inflammatory mucositis with or without increased

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peri-implant pocket probing depth. However, it can be difficult to assess the presence of peri-implant disease, because probing will result in penetration through the mucoperiosteum almost to the bone level, even if the tissues are healthy. This is because the gingival collagen fibres do not insert into the implant. The probing depth around implants is more dependent on the force used than for the gingival tissues of teeth (Gerber et al. 2009). For the same probing force, a deeper probing depth is found around implants than teeth; therefore, a probing force of 0.15 N (15 g) is recommended clinically for the peri-implant tissues. This study also showed that if the usual clinical probing force of 0.25 N (about 25 g) is used with implants, too many false-positive diagnoses of bleeding on probing resulted.

Koka and Zarb (2012) proposed a new concept of unsuccessful implant outcome as “osseoseparation”. Osseoseparation is used to describe stages of marginal bone loss and deepening pockets, with the implant eventually losing contact with bone (Koka and Zarb 2012). Peri-implant inflammation is not always present. In fact, the loss of osseointegration may not be associated with a gingival inflammatory reaction (Fig. 1.2). The terms “osseointegration” and “osseoseparation” therefore describe opposing biological phenomena. While the specific clinical and pathophysiological definitions determining osseointegration require further investigations, osseoseparation may indicate that long-term failure of implant therapy may be caused by a wide array of etiological factors that are currently unknown. Therefore, an accurate assessment protocol of long-term implant stability may need to be established.

## 1.2 What Is Meant by “Peri-implant Mucositis” and “Peri-implantitis”?

Peri-implant mucositis is a reversible inflammation of the soft tissues around an implant, whereas peri-implantitis is characterized by bone loss surrounding the implant. The failing implant may have increased mobility and an increased likelihood of a peri-implant radiolucency (Becker

et al. 1990). Peri-implant disease may result in bleeding from the marginal gingiva on gentle probing, but pus and late mobility usually indicate peri-implantitis. The clinical significance of the amount of bone lost in peri-implantitis will depend on the length of the implant that remains osseointegrated in the bone. The amount of bone loss can be assessed using a periapical radiograph. Peri-implantitis must be distinguished from the normal early bone remodelling that occurs after implant insertion. In the first year, this varies from 0.5 mm (Lindquist et al. 1988) to a little over 1.0 mm (Ahlqvist et al. 1990).

Definitions of peri-implantitis vary in the literature, but clinically, peri-implantitis is generally associated with suppuration and/or bleeding on probing with pocket depths  $\geq 5$  mm and marginal bone loss  $\geq 1.8$  mm (Charalampakis et al. 2011). Vertical bone defects are associated with a peri-implant pocket and are not usually painful.

Bleeding on probing is common, especially in elderly patients with implants, and in studies that have examined implants at least 5 years after insertion, the prevalence of disease is high. The percentage of individuals affected by peri-implant diseases will be influenced by the vigour and quality of the dentist’s maintenance regime and the patient’s motivation. One study found that 79.2 % of subjects with implants had peri-implant mucositis after 10 years and 56 % developed peri-implantitis (Roos-Jansaker et al. 2006). A further study found that 8.5 years after implant placement, the prevalence of mucositis and peri-implantitis in patients with implants was 31 and 37 %, respectively (Marrone et al. 2012). In those recruited into a dental practice-based study with at least 1 year implant loading, almost 40 % of patients had peri-implant mucositis and, in addition, about 16.3 % had peri-implantitis (Mir-Mari et al. 2012). Using a threshold of  $\geq 3$  threads of the implant exposed, which is equivalent to about 1.8 mm, it was found that a large proportion (28 % of 662 subjects) had one or more implants with progressive bone loss after 5 years of loading (Fransson et al. 2005). In one study, about 20.1 % of implant-supported fixed complete dental prostheses underwent peri-implant bone loss ( $>2$  mm) after 5 years and that this increased to 40.3 % after 10 years (Papaspyridakos et al. 2012).

Peri-implantitis may be characterized by a non-linear progression (Fransson et al. 2010), but only by prospectively following large numbers of patients with peri-implantitis over many years can the continuous or episodic nature of the disease be ascertained. Unfortunately, most studies are cross sectional in nature. Of more importance is the need for well-conducted observational studies that result in effective protocols for preventing peri-implant diseases. These high-quality studies would need to control for bias and confounding factors such as smoking; it is a misconception that larger studies are necessarily closer to the truth. Clinical trials that avoid bias have random allocation of patients to groups with examiners “blinded”, i.e. prevented from knowing which patients are in the experimental group and which are in the control group.

### 1.3 Changes in Implant Crestal Height: Platform Switching

In two-stage implants, the loss of crestal bone following implant exposure can cause esthetic problems. For clinical success this must not exceed 1.5 mm after 1 year (Albrektsson et al. 1986). Some consider that the micro-gap between the abutment and implant may become contaminated with bacteria and the resulting chronic inflammation causes bone resorption. The bone resorption would then re-establish a biological width around the implant. “Platform switching” uses smaller prosthetic components on top of wider-diameter implants to reposition the implant-abutment interface inwards towards the centre of the implant. The distance between the interface and the bone is increased, and the effect of any inflammation on the bone is reduced. There is no mechanical harm to reducing the abutment diameter by 0.5 mm, as assessed by finite element analysis (Pessoa et al. 2011). There is a much reduced vertical reduction in bone height compared with implants restored with a matching diameter of prosthetic components (Lazzara and Porter 2006). In a systematic review which included seven randomized controlled trials and three controlled clinical trials, bone loss was

significantly greater in the platform-matched group than in the platform-switched group, with a mean difference of  $-0.37$  mm (95 % CI  $-0.55$  to  $-0.20$ ) (Stafford 2012). The optimal size of the abutment-implant mismatch, the ideal abutment connection, and implant size are also unknown.

With two-part implants, the bone level forms 2 mm below the abutment-implant micro-gap. With one piece implants, the rough-smooth border should be positioned at the crestal bone level as this is where the bone level will eventually form (Hermann et al. 1997).

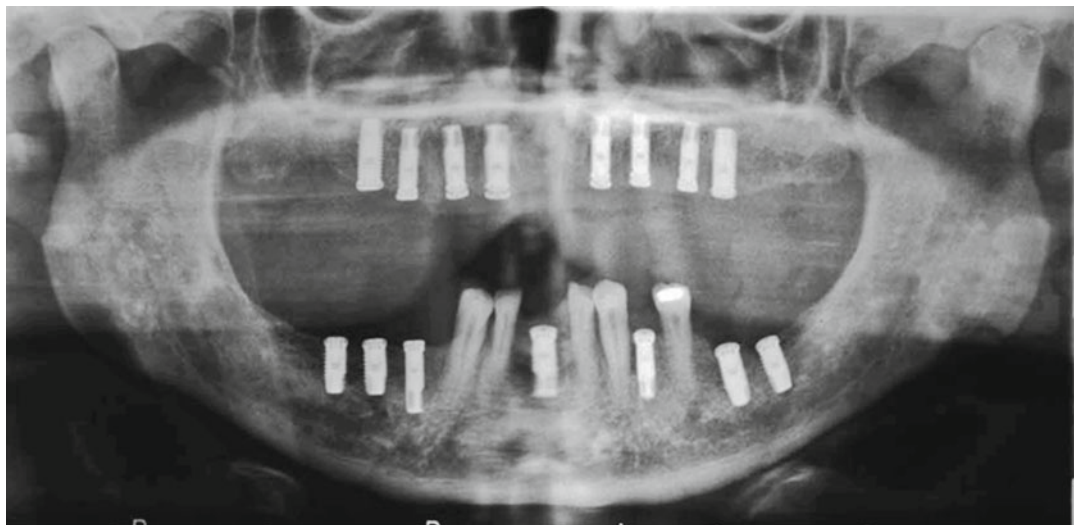
### 1.4 What Are the Other Causes of Marginal Bone Loss?

Other factors may also contribute to the crestal bone resorption, e.g. the presence of micro-threads, the roughness of the implants in the neck region and the type of implant-abutment connection (Shin et al. 2006). Early biomechanical stability may be also important in reducing early crestal bone loss, but even with fully integrated implants, excessive loading can result in micro-fracture and resorption of crestal bone. This could explain the higher marginal bone loss seen in the Brånemark® system with standard rather than with self-tapping fixtures (Quirynen et al. 1992). Using wide, barrel-necked implants can also cause compression of alveolar bone, which may accelerate marginal bone resorption (Duyck et al. 2010). With increasing misfit between the inserted metal implant and the prepared hole, bone fractures in the cortex are likely (Biliouris et al. 1989). The degree of misfit that can be safely tolerated will depend on the surgical skill used and the vascularity and stiffness of the host bone. When implants were placed in similar size and undersized preparations in the femurs of goats, no histologic differences were observed (Shalabi et al. 2007). However, an implantation period of only 12 weeks was used. In clinical studies, greater success has been achieved with the conventional technique (93 %) than with compression techniques (71.5 %) (Gulsahi et al. 2007), due to the reduced fracture and damage to the trabecular bone.

Rough-surfaced implants may also cause significantly less peri-implant bone loss than machined implants (Zechner et al. 2004), but this study used measurements from dental panoramic radiographs as the method of assessment. This imaging technique has a variable magnification, which is only minimized by careful patient positioning in the focal trough of the image. Panoramic radiographs may overestimate small losses in alveolar bone height (Semenoff et al. 2011). In a retrospective study, implants placed with flapless surgery were shown to have a comparable marginal bone loss to those placed following the raising of a mucoperiosteal flap (Nickenig et al. 2009), but again panoramic radiographs were used to assess the bone level. In addition, the median follow-up period was only 0.5 years (range 0.3–0.7 year), which is too short a time to allow any definitive conclusions to be made. At 3 years after loading, a Cochrane systematic review found that peri-implantitis occurred more frequently around rough-surfaced implants than with machined Branemark implants (Esposito et al. 2007).

## 1.5 Do Compromised, Healthy Teeth Survive Longer than Implants?

The survival of implants after 10 years is about 82–94 % which is similar to that of periodontally compromised but healthy teeth (Holm-Pedersen et al. 2007). Healthy teeth and implants that do not bleed on probing have an excellent prognosis. Where teeth have an increased gingival index, tooth loss is more likely (Schatzle et al. 2009). Where a tooth must be extracted, one option may be to replace the pontic with a fixed dental prosthesis using the natural teeth as abutments. These prostheses have an excellent survival rate of 90.4 % after 10 years and 80.5 % after 15 years (Bart et al. 2012), again comparable to the survival rate of implants. After 10 years, the annual failure rate of fixed dental prostheses that are tooth-supported (1.14 %) is also lower than those that are implant-supported (1.43 %) (Pjetursson et al. 2004). Multiple implants are also expensive, and studies involving detailed cost-benefit analysis are needed (Fig. 1.1).



**Fig. 1.1** Implants at time of placement

## 1.6 Does Previously Treated Periodontitis Influence Peri-implantitis?

Patients who have been previously treated for periodontitis and who are now receiving implants might be considered at increased risk of periodontitis compared with periodontally healthy patients. The bacteria associated with peri-implantitis are also present in periodontitis (Mombelli et al. 1987), and the teeth are the main reservoir of periodontal pathogens that subsequently colonize implants. It takes less than 2 weeks for the pathogenic bacteria associated with periodontitis to colonize the gingival sulci around implants when they are freshly uncovered for abutment connection (Quirynen et al. 2006). This occurs irrespective of the depth of the implant pockets or whether the patient rinses with chlorhexidine. But finding small numbers of potentially pathogenic bacteria within an implant pocket may have no clinical significance. It is the quantity of these periodontal pathogens not just their presence in the peri-implant sulcus that is clinically important. In a systematic review, it was concluded that patients with a history of treated periodontitis may suffer more implant loss, although caution was expressed about the high bias and lack of accounting for factors such as smoking in some of the studies (Ong et al. 2008). It is essential that patients with a previous history of treated periodontitis undergo comprehensive periodontal therapy following implant therapy and that implants with plaque-retentive or rough surfaces are avoided (Quirynen et al. 2007).

## 1.7 Do Systemic Factors Modify the Host Response to Plaque Around Implants?

Diabetes is known to exacerbate pre-existing periodontal disease and may be a risk factor in implant success. After 1 year, the failure rate of implants in diabetic patients is moderately

high at 7.3 % (Shernoff et al. 1994), but the failures in this study were not controlled for type of implant, patient's smoking status or other confounding factors. The success rate of implant treatment in diabetic patients can be improved by good glycaemic control with normalized serum glucose levels and glycated hemoglobin (or HbA1c) maintained at about 7 % (Marchand et al. 2012). A study of rough-surfaced implants placed by periodontology residents also showed that diabetes was associated with a moderately increased risk of failure (odds ratio of 2.59) (Zupnik et al. 2011). The heterogeneity of studies (with either short follow-up periods (Dowell et al. 2007) or small numbers of study participants (Farzad et al. 2002; Lambert et al. 2000; Cavalcanti et al. 2011)) has not permitted a meta-analysis (Bornstein et al. 2009).

Parafunctional habits and smoking are also known to exacerbate pre-existing periodontal disease and are a well-recognized risk factor in implant therapy. In a retrospective study undertaken 5 years after implant placement, 5.5 % of implants were found to have failed in 75 smokers, whereas only 2.9 % of implants failed in non-smokers (OR = 1.72) (Cavalcanti et al. 2011). Smoking is not related to a breakdown of osseointegration immediately following surgery but is rather associated with failure after uncovering the implant (Lambert et al. 2000). This would suggest that the deleterious outcome of smoking was the result of a toxic local effect, e.g. vasoconstriction, and therefore could be prevented by smoking cessation. The responsible agents may be the carbon monoxide, nicotine or other constituents of the particulate matter. A study involving 64 patients with at least 5 years of follow-up since they received their implants found greater marginal bone loss in smokers than non-smokers (Levin et al. 2008). The researcher examining the radiographs was unaware of the smoking status of the patients; however, there were only five who had smoked previously and six current smokers.



## 1.8 What Is the Role of Local Overload in Implant Failure?

Late implant failure is often associated with overload. Stress occurs to the upper part of the implant when lateral loads are applied (Klineberg et al. 2012). Many authors therefore recommend an occlusal scheme where loads are applied through the centre of the tooth as the patient closes into the intercuspal position. When finite element analysis was used to model a 5-unit fixed partial denture borne by 3 implants, it was found that group function produced excessive stresses compared with canine guidance (Gore and Evlioglu 2012). Therefore, the same occlusal principles described for fixed partial dentures involving teeth should be used for implant restorations.

### 1.8.1 How Do Osteocytes Respond to Loading?

At the cellular level, osteocytes may perform a mechanosensor role (“mechanostat”) and respond to strain in the bone by releasing cytokines. In this way the skeleton is able to adapt the bone form and size to its function in the most efficient manner. According to this hypothesis, low micro-strain is associated with bone resorption, whereas high micro-strain causes increased bone mass (Frost 1987). However, evidence to support this hypothesis has described raised cytokine levels in tissues surrounding failed knee prostheses, but this finding is related to the metal and polyethylene debris, and not to low-strain loading (Chiba et al. 1994). Based on in vitro data, one radical hypothesis suggested that the chemokine interleukin-8 is released into the gingival tissues by the contact of blood with the titanium implant surface and stimulates an additional inflammatory mucosal reaction which is independent of bacteria (Quabius et al. 2012). A study found no difference in the levels of interleukin-8 in the implant crevicular fluid of patients with peri-implantitis compared to those with healthy implants (Severino et al. 2011), but another study found increased levels (Luo et al. 2011). So far,

research has not elucidated the mechanism which determines whether bone loss or formation occurs with applied load, and pharmacological manipulation of the process cannot therefore be used.

### 1.8.2 The Bruxist Patient: Are Additional Precautions Necessary?

The clinical experience of many clinicians has made them cautious in implant treatment planning for patients with severe bruxism. Whether the excessive occlusal load directly or indirectly causes bone loss and implant failure is controversial. Animal studies have shown that excessive dynamic loads can cause marginal bone resorption and crater-like defects around tibial implants (Duyck et al. 2001), whereas static loads had no effect. The loads were applied 6 weeks after implant insertion, and with the implant site in a healing phase, this may have influenced the response to applied load. However, the clinical implication of this result is that the static loads introduced as a result of small casting errors may be tolerated, whereas excessive dynamic loads in chewing cause bone micro-fractures. Cyclic loading of the radius of dogs with excessive loads has been shown to cause bone micro-fractures that were significantly associated with resorption spaces (Burr et al. 1985). Micro-damage of bone can therefore initiate resorption.

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## 1.9 The Treatment of Compromised Teeth and Implants

Some authors recommend that periodontally compromised teeth be replaced with implants, but the alternative view is that these teeth should only be extracted as a last resort (Donos et al. 2012). Advanced periodontal disease can be successfully treated provided the patient can perform good plaque control. With regular maintenance care, extensive fixed cross-arch bridgework supported by a healthy but reduced amount of periodontal support (about 20 %) has been shown to be highly

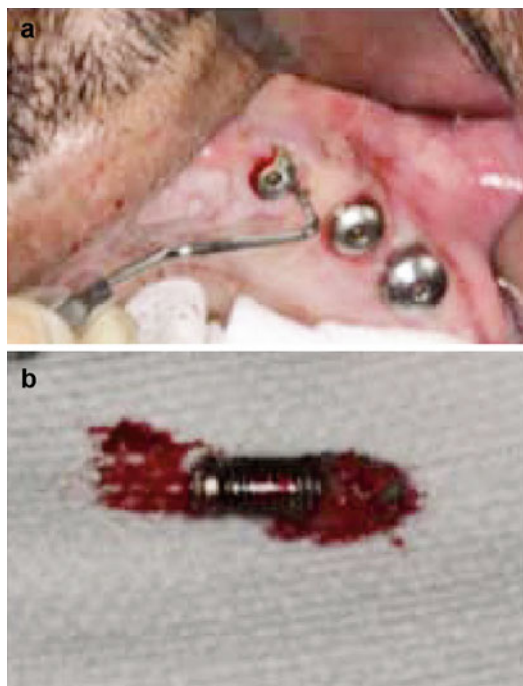
successful (Laurell et al. 1991). In a systematic review, meta-analysis showed that 92.9 % (95 % CI: 89.5–95.3 %) of fixed dental prostheses with a reduced but healthy periodontium survived (Lulic et al. 2007). This survival rate is similar to that of implant-supported prosthesis. In those situations requiring implant placement where teeth present a “hopeless” prognosis and require extraction as a result of periodontal disease, a vigorous maintenance programme should be instigated to prevent peri-implantitis. This is particularly so if the patient’s host response to plaque-induced disease makes them susceptible (see Chap. 4 which discusses the genetic background of implant failure).

A clear, universally accepted definition of peri-implantitis is necessary to allow comparisons between studies and to assess its prevalence. Peri-implant diseases are partially plaque-associated and so many of the classification systems used have similarities to those of gingivitis and periodontitis. A classification system for peri-implantitis has been proposed based on probing depth, the degree of bone loss around the implant and the presence of bleeding on probing (Froum and Rosen 2012). Implants can be lost with minimal evidence of associated gingival inflammation (Fig. 1.2).

Clinical parameters like probing depths greater than 6 mm, bleeding and/or suppuration on probing and radiographic evidence of bone loss can be utilized for diagnosing peri-implant diseases. Advanced peri-implantitis is classically associated with a trough of bone around the implant. The bone loss tends to increase with time and usually requires surgical treatment. Not surprisingly, patients who do not respond to periodontal maintenance therapy subsequently lose an increased number of implants (Fardal and Linden 2008).

### 1.9.1 Treatment of Peri-implant Disease: Nonsurgical Therapy

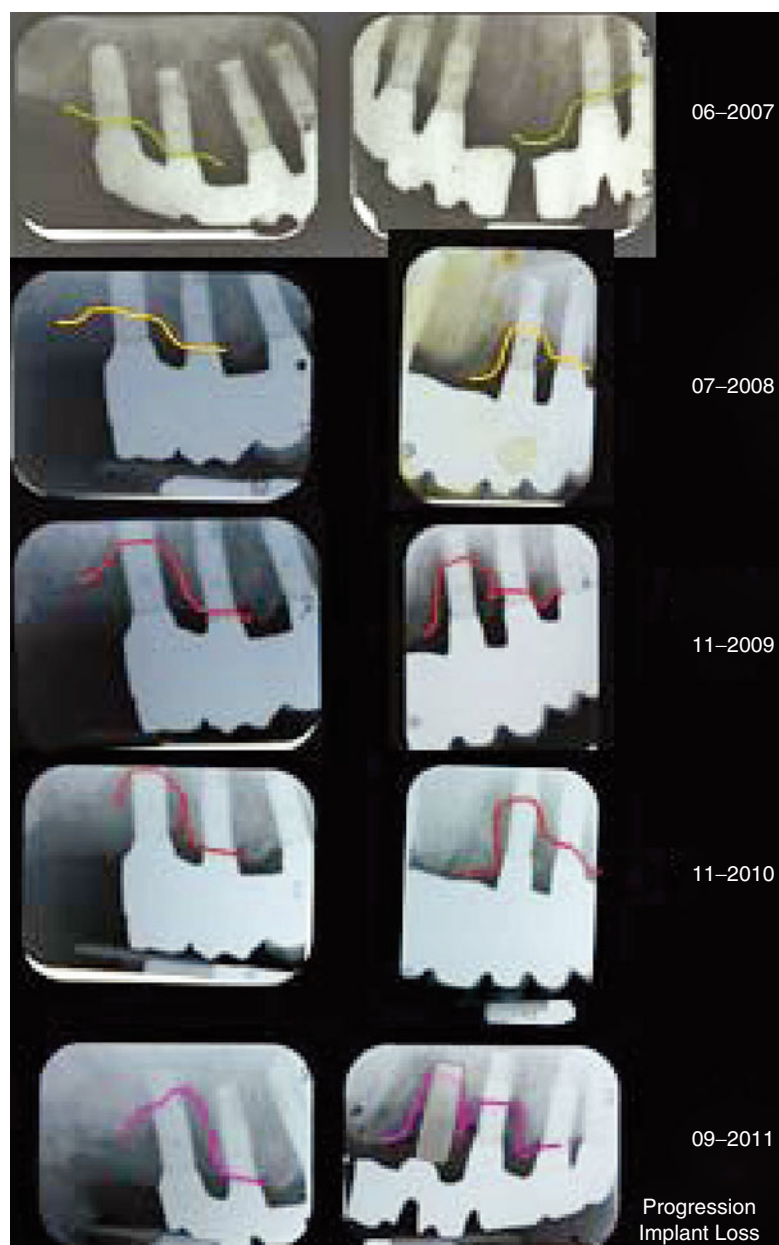
Many studies have found that the nonsurgical treatment of peri-implantitis does not produce predictable and sustained clinical improvement. In Fig. 1.3 and 1.4 continuous alveolar bone loss occurred despite regular implant surface debridement and oral hygiene instruction. The difficulty



**Fig. 1.2** (a) Deep pocket surrounding the implant despite the absence of gingival inflammation. (b) The implant required removal

arises for the dentist in cleaning a moderately roughened implant surface using traditional hand instruments. Similar difficulties occur for the patient in cleaning sub-gingival restoration margins. Air-abrasive devices provide short-term (6 months) improvement in probing depth and clinical attachment level when treating moderate degrees of peri-implantitis (Sahm et al. 2011). Other studies have found no improvement in probing pocket depth and bone levels with sub-gingival debridement using ultrasonic devices and curettes (Karring et al. 2005). In a small, randomized controlled trial (Heitz-Mayfield et al. 2011), nonsurgical debridement had some effect in reducing bleeding on probing around implants (healing was successful in 38 % of treated implants at 3 months), but brushing with chlorhexidine gel had no additive effect. Another short-term, 3-month study found a similar conclusion: that mechanical debridement was effective in reducing mucosal inflammation when implant pocket depths were less than 5 mm, but

**Fig. 1.3** Progression of implant bone loss over a 4-year period despite regular local debridement. The *colored lines* indicate the periodontal bone level



**Fig. 1.4** Peri-implant gingival inflammation



that chlorhexidine gel provided no additional benefit (Porras et al. 2002). There is also a tendency of chlorhexidine to cause staining and an altered taste sensation, but chlorhexidine gel does not harm the titanium surface when used as disinfecting agents (Ungvari et al. 2010).

In a 6-month oral hygiene programme, which recruited patients with mild peri-implantitis, an air-abrasive system was found to reduce the mean probing depth by about 0.5 mm (Sahm et al. 2011). These changes are not clinically significant and may result from the patient's improved oral hygiene rather than the air-abrasive intervention. In peri-implantitis, one application of an air-abrasive device or an erbium-doped yttrium, aluminium, and garnet (Er:YAG) laser was ineffective at reducing bacterial counts after 6 months or in showing any significant improvement in clinical parameters (Persson et al. 2011).

Peri-mucositis can be *prevented* by twice-daily use of an antiseptic mouthwash (Listerine, Warner-Lambert Co., NJ) when used as an adjunct to toothbrushing. This was shown in a double-blind, randomized clinical study that compared the antiseptic with a similar-tasting placebo mouthwash (Ciancio et al. 1995). This measure is simple, effective and readily accepted by patients. Listerine, hydrogen peroxide and chlorhexidine all have an antibacterial effect on oral biofilm microorganisms adhering to a titanium surface (Gosau et al. 2010), but their value in treating established peri-implant disease is in doubt. A 3 % hydrogen peroxide applied for 5 min or chlorhexidine gel solution applied for 5 min does not harm the titanium surface (Ungvari et al. 2010), but high-fluoride, acidic gels do cause corrosion of titanium (Stajer et al. 2008). These antiseptic solutions are supplemental measures because plaque must be mechanically removed, as failure to do so will result in bacterial recolonization of the biofilm.

### 1.9.2 Surgical Treatment of Peri-implantitis

Nonsurgical therapy does not provide successful results in the treatment of severe peri-implantitis but does have a place in establishing optimal gin-

gival tissue health prior to surgery. Residual pockets tend to remain and these usually require surgical elimination, but resective surgery can cause aesthetic problems in the anterior region of the mouth. A Cochrane review was unable to determine which technique was the most effective treatment for peri-implantitis (Esposito et al. 2006). This was because of problems in the reported clinical trials with small sample sizes, short follow-up periods, analysis based on implants and not patients and failures to report the initial severity of the peri-implantitis. In the absence of clear guidance from the available literature as to which treatment of peri-implantitis is superior, the clinician should use that intervention which has minimal side effects and cost.

In a study that undertook plaque control, pre-surgical antibiotics, surgical pocket elimination and bone recontouring, half of the patients (48 %) had no bleeding on probing after a short period of follow-up (up to 2 years) (Serino and Turri 2011). Treatment was more successful (74 %) in those implants with minor levels of initial bone loss compared with only 50 % for those implants with an initial bone loss of 5–6 mm. Treatment success is mainly dependent on the severity of bone loss around the implant. If bone loss around the implant is limited (at less than 2 mm), a nonsurgical treatment approach is recommended (Okayasu and Wang 2011). Peri-implant bone loss can be treated successfully with flap surgery, removal of granulation tissue and effective cleaning of the implant surface, resulting in successful repair in the majority of patients. One study reported a median defect depth reduction of 6.2 mm using this protocol (Behneke et al. 2000). However, re-osseointegration following surgery is unlikely. A histological study in dogs found that following guided tissue regeneration, “fine fibrillar material” formed adjacent to the implant surface (Schupbach et al. 1994). Treated implants become stabilized and are well adapted to new bone but are not osseointegrated. In a systematic review which included 17 articles, it was concluded that the most likely outcome from using bone grafting techniques and membranes is an incomplete filling of the bony defect (Sahrmann et al. 2011).

Preventing further peri-implant bone loss is challenging, especially when it is accompanied

by pocket depths >5 mm. Reports have documented the successful use of antimicrobial therapies combined with growth factors and guided tissue-regenerative membrane therapies (Froum et al. 2012). Membranes are used in surgery to stabilize the bone graft around the peri-implant defect. However, incorporating a membrane inevitably increases the complication rate in regenerative surgery. One study reported a loss of the membrane in 5 cases out of 42 augmentations due to infection, with further complications from membrane dehiscence (Gaggl and Schultes 1999). Membrane instability, exposure of the membrane or a failure to adequately remove bacterial contamination from the implant surface at surgery may be responsible for augmentation failure.

Many studies have reported the use of an air-powder cleaning device or citric acid to clean the implant surface. Air-powder systems and resin curettes result in far less surface alteration than using steel curettes or ultrasonic devices designed for cleaning teeth (Meschenmoser et al. 1996; Brookshire et al. 1997). Short, 5-s exposures to the air-abrasive system did not cause harmful changes to the implant surface, but longer 15-s exposures did roughen the implant surfaces (Chairay et al. 1997). It is difficult to make general clinical recommendations as different studies used different operating parameters, e.g. the air pressure of the device and the nature and particle size of the powder.

The use of antibiotics as the sole treatment of peri-implantitis has little support in the literature.

A variety of different antibiotic regimes have been recommended but with unpredictable outcomes. A systematic review found no evidence in favour of any particular antibiotic treatment protocol (Klinge et al. 2002). As with the treatment of chronic periodontitis, the resolution of peri-implantitis requires local debridement or curettage and regular plaque control, with antibiotics playing a less important role (Ericsson et al. 1996). Recolonization of the peri-implant pocket and further bone loss are inevitable without debridement.

It would be prudent for a clinician to start with the minimum treatment to debride the pocket and prevent further bone loss rather than with a more aggressive treatment that may be unpredictable.

### 1.10 Future Research Trends in Peri-implantitis

New clinical guidelines and antibacterial strategies need to be developed to manage peri-implantitis and its associated implant loss (Fig. 1.5). The biofilm that develops in peri-implantitis generally resembles that found in chronic periodontitis and mainly consists of gram-negative, anaerobic organisms. However, *Staphylococci*, *E. coli*, and *Candida* species are not normally associated with periodontitis but are found in a high proportion of peri-implantitis lesions (Leonhardt et al. 1999). Some of these organisms are resistant to antibiotics and antiseptics, and this may explain the inconsistent results that are found with various treatments of peri-implantitis. Paradoxically,



**Fig. 1.5** Peri-implant inflammation and bone loss (10-mm probing depth) and eventual implant loss

while manufacturers have designed implant surfaces to be an attractive environment for connective tissue, epithelial and bone cells, these surfaces are also easily colonized by bacterial cells. The result is that once a pathogenic bacterial biofilm becomes established, it is difficult to eliminate and treatment can often be unpredictable and unsatisfactory.

If the titanium oxide surface of the implant is modified to contain crystalline anatase, the surface has a reduced amount of bacterial adhesion (Del et al. 2005). Similarly, titanium surfaces modified with fluorine ions had a decreased growth of *P. gingivalis* and *A. actinomycetemcomitans* compared with the unmodified titanium surface (Yoshinari et al. 2001). The fluorine-modified surfaces had no deleterious effect on the proliferation of fibroblast cells in vitro. Fluoride ions were not released to cause an inhibitory effect; rather it was the metal fluoride surface that caused the antibacterial activity. However, the effect of this coating on osseointegration is untested.

Antiseptic coatings of titanium surfaces using chlorhexidine and chloroxylenol have been used in orthopaedic research where they provide antimicrobial infection for up to 8 weeks (Darouiche et al. 1998). However, this cannot be applied to the dental implant, as this requires a powerful antibacterial activity over a period of years. There has been some research to attempt to seal the oral environment from the implant interface with surface modification of abutment materials to allow peri-implant tissues (epithelial cell or fibroblasts) to adhere to these materials. This may render this junction less susceptible to future complications. The challenge for the future is to develop an implant surface which continuously prevents bacterial colonization and which does not affect osseointegration.

## References

- Ahlqvist J, Borg K, Gunne J, Nilson H, Olsson M, Astrand P (1990) Osseointegrated implants in edentulous jaws: a 2-year longitudinal study. *Int J Oral Maxillofac Implants* 5(2):155–163
- Albrektsson T, Zarb G, Worthington P, Eriksson AR (1986) The long-term efficacy of currently used dental implants: a review and proposed criteria of success. *Int J Oral Maxillofac Implants* 1(1):11–25
- Bart I, Dobler B, Schmidlin K, Zwahlen M, Salvi GE, Lang NP et al (2012) Complication and failure rates of tooth-supported fixed dental prostheses after 7 to 19 years in function. *Int J Prosthodont* 25(4):360–367
- Becker W, Becker BE, Newman MG, Nyman S (1990) Clinical and microbiologic findings that may contribute to dental implant failure. *Int J Oral Maxillofac Implants* 5(1):31–38
- Behneke A, Behneke N, d' Hoedt B (2000) Treatment of peri-implantitis defects with autogenous bone grafts: six-month to 3-year results of a prospective study in 17 patients. *Int J Oral Maxillofac Implants* 15(1):125–138
- Biliouris TL, Schneider E, Rahn BA, Gasser B, Perren SM (1989) The effect of radial preload on the implant-bone interface: a cadaveric study. *J Orthop Trauma* 3(4):323–332
- Bornstein MM, Cionca N, Mombelli A (2009) Systemic conditions and treatments as risks for implant therapy. *Int J Oral Maxillofac Implants* 24(Suppl):12–27
- Brookshire FV, Nagy WW, Dhuru VB, Ziebert GJ, Chada S (1997) The qualitative effects of various types of hygiene instrumentation on commercially pure titanium and titanium alloy implant abutments: an in vitro and scanning electron microscope study. *J Prosthet Dent* 78(3):286–294
- Burr DB, Martin RB, Schaffler MB, Radin EL (1985) Bone remodeling in response to in vivo fatigue micro-damage. *J Biomech* 18(3):189–200
- Cavalcanti R, Oreglia F, Manfredonia MF, Gianserra R, Esposito M (2011) The influence of smoking on the survival of dental implants: a 5-year pragmatic multicentre retrospective cohort study of 1727 patients. *Eur J Oral Implantol* 4(1):39–45
- Chairay JP, Boulekbache H, Jean A, Soyer A, Bouchard P (1997) Scanning electron microscopic evaluation of the effects of an air-abrasive system on dental implants: a comparative in vitro study between machined and plasma-sprayed titanium surfaces. *J Periodontol* 68(12):1215–1222
- Charalampakis G, Rabe P, Leonhardt A, Dahlen G (2011) A follow-up study of peri-implantitis cases after treatment. *J Clin Periodontol* 38(9):864–871
- Chiba J, Schwendeman LJ, Booth RE Jr, Crossett LS, Rubash HE (1994) A biochemical, histologic, and immunohistologic analysis of membranes obtained from failed cemented and cementless total knee arthroplasty. *Clin Orthop Relat Res* 299:114–124
- Ciancio SG, Lauciello F, Shibly O, Vitello M, Mather M (1995) The effect of an antiseptic mouthrinse on implant maintenance: plaque and peri-implant gingival tissues. *J Periodontol* 66(11):962–965
- Darouiche RO, Green G, Mansouri MD (1998) Antimicrobial activity of antiseptic-coated orthopaedic devices. *Int J Antimicrob Agents* 10(1):83–86
- Del CB, Brunella MF, Giordano C, Peddeferrri MP, Valtulina V, Visai L et al (2005) Decreased bacterial adhesion to

- surface-treated titanium. *Int J Artif Organs* 28(7):718–730
- Donos N, Laurell L, Mardas N (2012) Hierarchical decisions on teeth vs. implants in the periodontitis-susceptible patient: the modern dilemma. *Periodontol* 2000 59(1):89–110
- Dowell S, Oates TW, Robinson M (2007) Implant success in people with type 2 diabetes mellitus with varying glycemic control: a pilot study. *J Am Dent Assoc* 138(3):355–361
- Duyck J, Ronold HJ, Van OH, Naert I, Vander SJ, Ellingsen JE (2001) The influence of static and dynamic loading on marginal bone reactions around osseointegrated implants: an animal experimental study. *Clin Oral Implants Res* 12(3):207–218
- Duyck J, Corpas L, Vermeiren S, Ogawa T, Quirynen M, Vandamme K et al (2010) Histological, histomorphometrical, and radiological evaluation of an experimental implant design with a high insertion torque. *Clin Oral Implants Res* 21(8):877–884
- Ericsson I, Persson LG, Berglundh T, Edlund T, Lindhe J (1996) The effect of antimicrobial therapy on periimplantitis lesions. An experimental study in the dog. *Clin Oral Implants Res* 7(4):320–328
- Esposito M, Grusovin MG, Coulthard P, Worthington HV (2006) Interventions for replacing missing teeth: treatment of perimplantitis. *Cochrane Database Syst Rev* (3):CD004970
- Esposito M, Murray-Curtis L, Grusovin MG, Coulthard P, Worthington HV (2007) Interventions for replacing missing teeth: different types of dental implants. *Cochrane Database Syst Rev* (4):CD003815
- Fardal O, Linden GJ (2008) Tooth loss and implant outcomes in patients refractory to treatment in a periodontal practice. *J Clin Periodontol* 35(8):733–738
- Farzad P, Andersson L, Nyberg J (2002) Dental implant treatment in diabetic patients. *Implant Dent* 11(3):262–267
- Fransson C, Lekholm U, Jemt T, Berglundh T (2005) Prevalence of subjects with progressive bone loss at implants. *Clin Oral Implants Res* 16(4):440–446
- Fransson C, Tomasi C, Pikner SS, Grondahl K, Wennstrom JL, Leyland AH et al (2010) Severity and pattern of peri-implantitis-associated bone loss. *J Clin Periodontol* 37(5):442–448
- Frost HM (1987) Bone “mass” and the “mechanostat”: a proposal. *Anat Rec* 219(1):1–9
- Froum SJ, Rosen PS (2012) A proposed classification for peri-implantitis. *Int J Periodontics Restorative Dent* 32(5):533–540
- Froum SJ, Froum SH, Rosen PS (2012) Successful management of peri-implantitis with a regenerative approach: a consecutive series of 51 treated implants with 3- to 7.5-year follow-up. *Int J Periodontics Restorative Dent* 32(1):11–20
- Gaggl A, Schultes G (1999) Titanium foil-guided tissue regeneration in the treatment of periimplant bone defects. *Implant Dent* 8(4):368–375
- Gerber JA, Tan WC, Balmer TE, Salvi GE, Lang NP (2009) Bleeding on probing and pocket probing depth in relation to probing pressure and mucosal health around oral implants. *Clin Oral Implants Res* 20(1):75–78
- Gore E, Evlioglu G (2012) Assessment of the effect of two occlusal concepts for implant-supported fixed prostheses by Finite Element Analysis in patients with bruxism. *J Oral Implantol* 2012 Jan 15. doi: <http://dx.doi.org/10.1563/AAID-JOI-D-11-00044>. [Epub ahead of print].
- Gosau M, Hahnel S, Schwarz F, Gerlach T, Reichert TE, Burgers R (2010) Effect of six different peri-implantitis disinfection methods on in vivo human oral biofilm. *Clin Oral Implants Res* 21(8):866–872
- Gulsahi A, Paksoy CS, Yazicioglu N, Arpak N, Kucuk NO, Terzioğlu H (2007) Assessment of bone density differences between conventional and bone-condensing techniques using dual energy x-ray absorptiometry and radiography. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 104(5):692–698
- Heitz-Mayfield LJ, Salvi GE, Botticelli D, Mombelli A, Faddy M, Lang NP (2011) Anti-infective treatment of peri-implant mucositis: a randomised controlled clinical trial. *Clin Oral Implants Res* 22(3):237–241
- Hermann JS, Cochran DL, Nummikoski PV, Buser D (1997) Crestal bone changes around titanium implants. A radiographic evaluation of unloaded nonsubmerged and submerged implants in the canine mandible. *J Periodontol* 68(11):1117–30
- Holm-Pedersen P, Lang NP, Muller F (2007) What are the longevities of teeth and oral implants? *Clin Oral Implants Res* 18(Suppl 3):15–19
- Karring ES, Stavropoulos A, Ellegaard B, Karring T (2005) Treatment of peri-implantitis by the vector system. *Clin Oral Implants Res* 16(3):288–293
- Klineberg IJ, Trulsson M, Murray GM (2012) Occlusion on implants – is there a problem? *J Oral Rehabil* 39(7):522–537
- Klinge B, Gustafsson A, Berglundh T (2002) A systematic review of the effect of anti-infective therapy in the treatment of peri-implantitis. *J Clin Periodontol* 29(Suppl 3):213–225
- Koka S, Zarb G (2012) On osseointegration: the healing adaptation principle in the context of osseosufficiency, osseoseparation, and dental implant failure. *Int J Prosthodont* 25(1):48–52
- Lambert PM, Morris HF, Ochi S (2000) The influence of smoking on 3-year clinical success of osseointegrated dental implants. *Ann Periodontol* 5(1):79–89
- Laurell L, Lundgren D, Falk H, Hugoson A (1991) Long-term prognosis of extensive polyunit cantilevered fixed partial dentures. *J Prosthet Dent* 66(4):545–52
- Lazzara RJ, Porter SS (2006) Platform switching: a new concept in implant dentistry for controlling postrestorative crestal bone levels. *Int J Periodontics Restorative Dent* 26(1):9–17
- Leonhardt A, Renvert S, Dahlen G (1999) Microbial findings at failing implants. *Clin Oral Implants Res* 10(5):339–345
- Levin L, Hertzberg R, Har-Nes S, Schwartz-Arad D (2008) Long-term marginal bone loss around single



- dental implants affected by current and past smoking habits. *Implant Dent* 17(4):422–429
- Lindquist LW, Rockler B, Carlsson GE (1988) Bone resorption around fixtures in edentulous patients treated with mandibular fixed tissue-integrated prostheses. *J Prosthet Dent* 59(1):59–63
- Lulic M, Bragger U, Lang NP, Zwahlen M, Salvi GE (2007) Ante's (1926) law revisited: a systematic review on survival rates and complications of fixed dental prostheses (FDPs) on severely reduced periodontal tissue support. *Clin Oral Implants Res* 18(Suppl 3):63–72
- Luo L, Xie P, Gong P, Tang XH, Ding Y, Deng LX (2011) Expression of HMGB1 and HMGN2 in gingival tissues, GCF and PICF of periodontitis patients and peri-implantitis. *Arch Oral Biol* 56(10):1106–1111
- Marchand F, Raskin A, Onnes-Hornes A, Barry T, Dubois N, Valero R et al (2012) Dental implants and diabetes: conditions for success. *Diabetes Metab* 38(1):14–19
- Marrone A, Lasserre J, Bercy P, Brecx MC (2012) Prevalence and risk factors for peri-implant disease in Belgian adults. *Clin Oral Implants Res* 2012 May 3. doi: [10.1111/j.1600-0501.2012.02476.x](https://doi.org/10.1111/j.1600-0501.2012.02476.x). [Epub ahead of print]
- Meschenmoser A, d'Hoedt B, Meyle J, Ellsner G, Korn D, Hammerle H et al (1996) Effects of various hygiene procedures on the surface characteristics of titanium abutments. *J Periodontol* 67(3):229–235
- Mir-Mari J, Mir-Orfila P, Figueiredo R, Valmaseda-Castellon E, Gay-Escoda C (2012) Prevalence of peri-implant diseases. A cross-sectional study based on a private practice environment. *J Clin Periodontol* 39(5):490–494
- Mombelli A, van Oosten MA, Schurch E Jr, Lang NP (1987) The microbiota associated with successful or failing osseointegrated titanium implants. *Oral Microbiol Immunol* 2(4):145–151
- Nickenig HJ, Wichmann M, Schlegel KA, Nkenke E, Eitner S (2009) Radiographic evaluation of marginal bone levels adjacent to parallel-screw cylinder machined-neck implants and rough-surfaced micro-threaded implants using digitized panoramic radiographs. *Clin Oral Implants Res* 20(6):550–554
- Okayasu K, Wang HL (2011) Decision tree for the management of periimplant diseases. *Implant Dent* 20(4):256–261
- Ong CT, Ivanovski S, Needleman IG, Retzepi M, Moles DR, Tonetti MS et al (2008) Systematic review of implant outcomes in treated periodontitis subjects. *J Clin Periodontol* 35(5):438–462
- Papaspyridakos P, Chen CJ, Chuang SK, Weber HP, Gallucci GO (2012) A systematic review of biologic and technical complications with fixed implant rehabilitations for edentulous patients. *Int J Oral Maxillofac Implants* 27(1):102–110
- Persson GR, Roos-Jansaker AM, Lindahl C, Renvert S (2011) Microbiologic results after non-surgical erbium-doped:yttrium, aluminum, and garnet laser or air-abrasive treatment of peri-implantitis: a randomized clinical trial. *J Periodontol* 82(9):1267–1278
- Pessoa RS, Coelho PG, Muraru L, Marcantonio E Jr, Vaz LG, Vander SJ et al (2011) Influence of implant design on the biomechanical environment of immediately placed implants: computed tomography-based nonlinear three-dimensional finite element analysis. *Int J Oral Maxillofac Implants* 26(6):1279–1287
- Pjetursson BE, Tan K, Lang NP, Bragger U, Egger M, Zwahlen M (2004) A systematic review of the survival and complication rates of fixed partial dentures (FPDs) after an observation period of at least 5 years. *Clin Oral Implants Res* 15(6):667–676
- Porras R, Anderson GB, Caffesse R, Narendran S, Trejo PM (2002) Clinical response to 2 different therapeutic regimens to treat peri-implant mucositis. *J Periodontol* 73(10):1118–1125
- Quabius ES, Ossenkop L, Harder S, Kern M (2012) Dental implants stimulate expression of Interleukin-8 and its receptor in human blood—an in vitro approach. *J Biomed Mater Res B Appl Biomater* 100(5):1283–1288
- Quirynen M, Naert I, van Steenberghe D (1992) Fixture design and overload influence marginal bone loss and fixture success in the Branemark system. *Clin Oral Implants Res* 3(3):104–111
- Quirynen M, Vogels R, Peeters W, van Steenberghe D, Naert I, Haffajee A (2006) Dynamics of initial subgingival colonization of 'pristine' peri-implant pockets. *Clin Oral Implants Res* 17(1):25–37
- Quirynen M, Abarca M, Van Assche N, Nevins M, van Steenberghe D (2007) Impact of supportive periodontal therapy and implant surface roughness on implant outcome in patients with a history of periodontitis. *J Clin Periodontol* 34(9):805–815
- Roos-Jansaker AM, Lindahl C, Renvert H, Renvert S (2006) Nine- to fourteen-year follow-up of implant treatment. Part II: presence of peri-implant lesions. *J Clin Periodontol* 33(4):290–295
- Sahm N, Becker J, Santel T, Schwarz F (2011) Non-surgical treatment of peri-implantitis using an air-abrasive device or mechanical debridement and local application of chlorhexidine: a prospective, randomized, controlled clinical study. *J Clin Periodontol* 38(9):872–878
- Sahrman P, Attin T, Schmidlin PR (2011) Regenerative treatment of peri-implantitis using bone substitutes and membrane: a systematic review. *Clin Implant Dent Relat Res* 13(1):46–57
- Sanz M, Alandez J, Lazaro P, Calvo JL, Quirynen M, van Steenberghe D (1991) Histo-pathologic characteristics of peri-implant soft tissues in Branemark implants with 2 distinct clinical and radiological patterns. *Clin Oral Implants Res* 2(3):128–134
- Schatzle M, Faddy MJ, Cullinan MP, Seymour GJ, Lang NP, Burgin W et al (2009) The clinical course of chronic periodontitis: V. Predictive factors in periodontal disease. *J Clin Periodontol* 36(5):365–371
- Schupbach P, Hürzeler M, Grunder U (1994) Implant-tissue interfaces following treatment of peri-implantitis

- using guided tissue regeneration: a light and electron microscopic study. *Clin Oral Implants Res* 5(2):55–65
- Semenoff L, Semenoff TA, Pedro FL, Volpato ER, Machado MA, Borges AH et al (2011) Are panoramic radiographs reliable to diagnose mild alveolar bone resorption? *ISRN Dent* 2011:363578
- Serino G, Turri A (2011) Outcome of surgical treatment of peri-implantitis: results from a 2-year prospective clinical study in humans. *Clin Oral Implants Res* 22(11):1214–1220
- Severino VO, Napimoga MH, de Lima Pereira SA (2011) Expression of IL-6, IL-10, IL-17 and IL-8 in the peri-implant crevicular fluid of patients with peri-implantitis. *Arch Oral Biol* 56(8):823–828
- Shalabi MM, Wolke JG, de Ruijter AJ, Jansen JA (2007) Histological evaluation of oral implants inserted with different surgical techniques into the trabecular bone of goats. *Clin Oral Implants Res* 18(4):489–495
- Shernoff AF, Colwell JA, Bingham SF (1994) Implants for type II diabetic patients: interim report. VA Implants in Diabetes Study Group. *Implant Dent* 3(3):183–185
- Shin YK, Han CH, Heo SJ, Kim S, Chun HJ (2006) Radiographic evaluation of marginal bone level around implants with different neck designs after 1 year. *Int J Oral Maxillofac Implants* 21(5):789–794
- Stafford GL (2012) Evidence supporting platform-switching to preserve marginal bone levels not definitive. *Evid Based Dent* 13(2):56–57
- Stajer A, Ungvari K, Pelsoczi IK, Polyanka H, Oszko A, Mihalik E et al (2008) Corrosive effects of fluoride on titanium: investigation by X-ray photoelectron spectroscopy, atomic force microscopy, and human epithelial cell culturing. *J Biomed Mater Res A* 87(2):450–458
- Ungvari K, Pelsoczi IK, Kormos B, Oszko A, Rakonczay Z, Kemeny L et al (2010) Effects on titanium implant surfaces of chemical agents used for the treatment of peri-implantitis. *J Biomed Mater Res B Appl Biomater* 94(1):222–229
- Yoshinari M, Oda Y, Kato T, Okuda K (2001) Influence of surface modifications to titanium on antibacterial activity in vitro. *Biomaterials* 22(14):2043–2048
- Zechner W, Trinkl N, Watzak G, Busenlechner D, Tepper G, Haas R et al (2004) Radiologic follow-up of peri-implant bone loss around machine-surfaced and rough-surfaced interforaminal implants in the mandible functionally loaded for 3 to 7 years. *Int J Oral Maxillofac Implants* 19(2):216–221
- Zupnik J, Kim SW, Ravens D, Karimbux N, Guze K (2011) Factors associated with dental implant survival: a 4-year retrospective analysis. *J Periodontol* 82(10):1390–1395

# The Response of the Bone and the Implant to Loading

2

Hugh Devlin

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## 2.1 Biomechanical Aspects of Implants and Why They Fail

Minimising the interfacial forces between implant and bone is essential to implant success. This is especially important in situations such as the cantilevered implant-supported prosthesis where the loads are increased two- or threefold compared with those stresses detected on a single implant (McAlarney and Stavropoulos 1996; Osier 1991). Excessive loading can cause bone resorption, screw fracture and implant loss. Cantilevered implant-supported prostheses allow restoration of an edentulous space particularly where insufficient bone exists for implant placement. Where the pontic size is small (of the size of a premolar tooth) and protected in lateral excursive movements, the evidence from the published literature is that these cantilevered restorations have an excellent success rate. For example, in a systematic review by Aglietta et al. (2009), the 10-year survival for implant-supported cantilevered restorations was 88.9 % (95 % CI=70.8–96.1 %), which is comparable to tooth-supported bridges.

Occlusal loads are unfavourable in implant-supported overdentures and cantilevered restorations. The latter is a successful type of restoration, and if the loads applied to the implants are comparable in both clinical situations, should the overdenture also be equally successful? In the maxilla, a high failure rate has been reported with these overdentures (Andreietelli et al. 2010; Hutton et al. 1995). This is due to a variety of factors.

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Often, maxillary implant-supported overdentures are opposed by the natural lower dentition so that the biting loads applied are high. In addition, the occlusal loads are often applied at an angle to the long axis of the implant due to the necessity to place the implant in a sufficient bulk of bone.

Studies have shown that immediate loading of unsplinted mandibular implants retaining an overdenture is a successful treatment (Liao et al. 2010; Roe et al. 2011). With immediate loading, the effects of a slight misfit of the prosthesis are minimal as stresses applied to the implant are dissipated by bone resorption during early healing.

## 2.2 Bone Quality

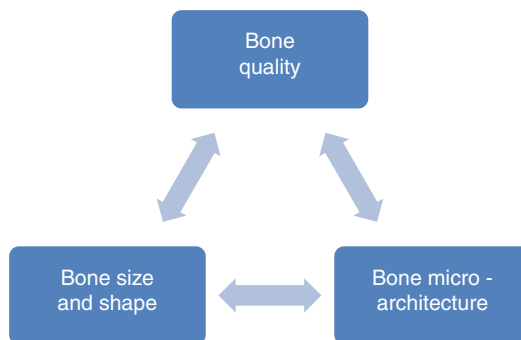
Bone quality refers to those factors of bone which are important in assessing its ability to resist load and therefore allow successful implant osseointegration. There are many interrelated factors which determine bone quality, but bone size and shape and the micro-architecture of the bone are important (Fig. 2.1). Excessive resorption of cancellous bone can occur after the menopause, causing thinning or loss of trabeculae, and in cortical bone there is increased porosity. Bell et al. (2000) found that cortical porosity was a principal feature in patients with hip fractures. This suggests that if dentists can identify cortical porosity in dental panoramic radiographs, then they may be able to identify those at high risk of a hip fracture. Rigorous assessment of cancellous bone architecture depends on evaluating the trabecular number, thickness and spacing. Dense cancellous bone will have many connected trabeculae and small marrow spaces (Gomes de Oliveira et al. 2012).

The commonest system used to classify a patient's quality of bone at the implant site is that proposed by Lekholm and Zarb (1985). This classification of bone is divided into four groups:

Type 1 – mostly dense cortical bone

Type 2 – a thick cortical layer surrounds dense cancellous bone

Type 3 – a thin cortical layer surrounds dense cancellous bone



**Fig. 2.1** Bone quality includes bone size, shape and bone microarchitecture

Type 4 – a thin cortical layer surrounds cancellous bone of low density

A sufficient amount and density of host bone is essential to implant success, which is reduced if there is a lack of stability at insertion. There is a general consensus that a minimum width of 5 mm of alveolar bone is essential for long-term implant success, with narrow ridges requiring augmentation. All commercially available implant systems have an impressive success rate exceeding 85 % after 5-year follow-up (Lekholm 1992), and selection of patients with adequate bone volume, density and architecture is critically important in determining success. Finite element analysis has shown that bone-implant strain increased with decreasing bone quality (Lin et al. 2008). However, this may not be clinically important to implant survival given the excellent implant success rate (97 % in the maxillae and 97.3 % in the mandible) achieved in patients with osteoporosis of either the hip or spine, or both (Friberg et al. 2001), assuming that the jaw bone density was also reduced in these patients. Earlier studies have shown that implant failure was related to their placement in low-density bone (especially in the maxilla) (Friberg et al. 1991), but recent improvements in implant surfaces may improve the chances of osseointegration in poor-quality bone and prevent their failure.

Figure 2.2a illustrates a dental panoramic tomogram of a 45-year-old female patient with generalised chronic periodontal disease and periapical radiolucencies affecting some of the lower



teeth. Over a period of 10 years, she suffered failure of her implants and lost more teeth. This was followed by severe residual ridge resorption (Fig. 2.2b).

In Fig. 2.2c, the lower mandibular cortical border from a patient aged 45 years appears to have a smooth superior border (see arrows), whereas the cortical border of the later image when the patient was aged 55 years appears irregular and porous (Fig. 2.2d). The thinning and increasing porosity of the lower cortical border has been described as a sign of systemic bone loss in postmenopausal osteoporosis. Whether the reduced mandibular bone density played any causative role in the loss of this patient's implants and teeth is unknown. This is because there are a large number of other potentially important variables that can influence tooth loss, e.g. oral hygiene and medical history of the patient.

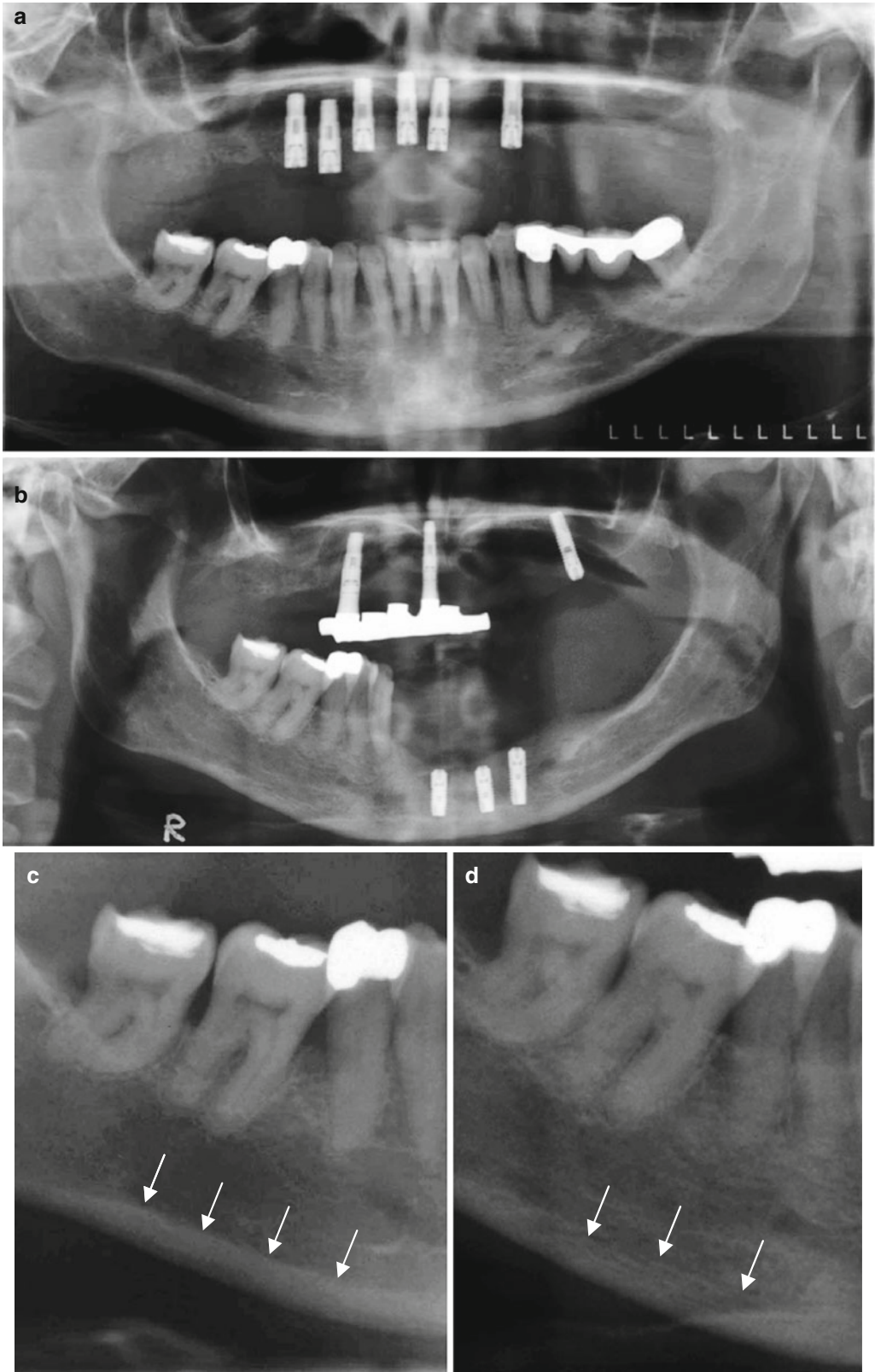
### 2.2.1 Bone Quality, Gender and Age

Roberts et al. (2011) showed that women undergo little change in mandibular cortical width until the age of about 42 years, after which the cortex starts to thin at an increasingly faster (quadratic) rate. The mean smoothed mandibular cortical width in their sample was shown to be higher for adult men than women, but this is not reflected in any major difference in the failure rates of implants between genders. In a study by Jang et al. (2011), they placed 6,385 implants in 3,755 patients, but the sample had 3,120 males and a much smaller number of females, 635. Data from their figures suggested that older women had a poorer implant survival after 80 months, but there was no statistically significant effect of gender. The effect of gender was also analysed in a study of implant survival in bone grafts used for the treatment of severe alveolar ridge resorption (Schliephake et al. 1997). There was a high failure rate in older women, aged 51–60 years, who were reconstructed with an iliac crest onlay and simultaneous placement of endosseous implants. The iliac crest graft and recipient site may have been of poor quality, given the decline in bone

density that occurs following the menopause. Advanced age has been shown to increase implant failure risk, but this may relate to the decline in jaw bone density which occurs with age. In a study by Moy et al. (2005), their 60–79 age group had a significantly higher risk of implant failure ( $RR=2.24$ ;  $P<0.05$ ), but this age effect was not significant at older ages (>79 years) perhaps due to a reduced sample size in this group.

Bone volume and density are two of the most important factors that determine the duration of healing before implants can be loaded. The original Brånemark protocol recommended a two-staged approach with placement of the implants in bone and subsequent surgical exposure after 3 months in the mandible and 6 months in the maxilla. The difference in the time of implant submergence relates to the fine trabecular bone and thin cortical structure of the maxilla compared to the mandible. Despite this, the failure rate of maxillary implants tends to be higher than in the mandible. Weng et al. (2003) in a prospective, multicentre study found that 33 % of failures were associated with machined surface implants placed in the posterior maxilla, with a success rate of only 80.6 %. Multiple factors can combine to reduce the success rate of implants in this region, such as a higher occlusal loading, a reduced volume of available bone and a reduced bone density. Overall, their implant success rate was 91.1 %, which is comparable to most other implant studies. Buser et al. (1991) later showed that 96.2 % of one-stage, non-submerged ITI implants (International Team for Oral Implantology, Institut Straumann AG, Waldenburg, Switzerland) osseointegrated successfully after a follow-up period of 3 years. This study confirmed that non-submerged implants had an excellent success rate when placed in good-quality bone.

Immediate loading of implants placed in the mandible had a 98.4 % success rate in a retrospective study by Kacer et al. (2010). They recommended that immediate loading be considered in the mandible where primary stability of the implant was greater than 35 N-cm. In a 5-year retrospective study, Malo et al. (2011) placed 995 immediately loaded implants in 221 edentulous



patients and found that females lost more implants than males.

Implants have been also shown to have a better survival if placed in native maxillary bone than if augmented bone is used (Lambert et al. 2009). This relates to the lack of primary implant stability at insertion. With reduced bone quality or poor surgical technique, a two-stage surgical approach has a better prognosis than immediately loading the implant (Esposito et al. 2009). Precise drilling of the bone to the correct diameter for the implant is required; otherwise, good primary stability is not possible.

### 2.2.2 Imaging Modalities Available to Assess Bone Quality

Newer techniques such as microcomputed tomography may allow assessment of bone structure but are still at the experimental stage. Techniques such as dual energy X-ray absorptiometry can measure mandibular bone density (Devlin and Horner 2007), but assessing bone quality requires analysis of bone architecture. In one preliminary study, the trabecular bone volume and implant stability (measured using resonance frequency analysis) were not significantly correlated, but this may be due to the small sample size (23 implant sites of 10 patients).

Conventional dental panoramic tomograms are often used to assess the likelihood of damage of anatomical structures adjacent to the path of the implant placement and the height of the available bone. Magnification and distortion of the image may occur, which introduces an element of inaccuracy in treatment planning. Cone beam computed tomography (CBCT) provides an opportunity for 3D viewing of the jaws with no image magnification and therefore is most useful in diagnosis and treatment planning.

Much of the literature surrounding CBCT has shown good accuracy and repeatability of measurements in laboratory settings. However, these results are not directly applicable to the clinical situation where minor patient movement can produce inaccuracy. With many potential clinical applications of CBCT, its value needs to be assessed against whether it improves the quality of treatment outcome for most patients. CBCT is certainly useful in those situations requiring cross-sectional imaging, e.g. where there is some doubt about the position of the inferior alveolar nerve or the shape of the residual alveolar ridge.

There is considerable controversy as to whether CBCT bone radiodensity values (as measured by Hounsfield units) are correlated with other measurements of bone density. Fuster-Torres et al. (2011) found a significant correlation between CBCT-derived bone density values and insertion torque measurements for implant sites in the anterior mandible. Others have reported similar correlations between implant torque resistance and radiographic density evaluation using CBCT (Lee et al. 2007) or computed tomography Hounsfield units (Turkyilmaz et al. 2006). However, a major source of error in assessing jaw bone density arises from the variation in the amount of fat between the bone trabeculae at different jaw sites. Hounsfield units (HU) use the radiodensity of water as the zero on the scale, and a typical value for cancellous bone radiodensity is 700 HU, air is -1,000 HU and fat is -50 to -100 HU. If the jaw has a high fat content, the reading in HU will be reduced and therefore will not provide a true representation of the bone content. Similarly, there has been variation in intensity values reported in CBCT images which is dependent on the particular device, the precise imaging parameters and the

**Fig. 2.2** (a) The dental panoramic tomogram of a patient who then underwent extensive implant therapy over the next 10 years. (b) The patient had severe residual ridge resorption following tooth extraction and loss of implants. (c) The superior border of the mandibular cortex appears even and unresorbed at age 45 years. (d) At age 55 years,

the mandibular cortical bone has become porous and thinned. The superior cortical border is uneven. One cannot conclude that the osteoporotic bone changes are causing the implant loss and the residual ridge resorption, but they may be important

positioning of the field of view (Nackaerts et al. 2011).

CBCT may be useful in assessing the cross-sectional shape of the residual ridge prior to implant placement and in other situations where clinical doubt exists as to the position of the maxillary sinus and important neurovascular structures. Haemorrhage involving the floor of the mouth is particularly serious where it can compromise the airway.

The CBCT data can also be used to construct templates that are employed to guide implant placement.

## 2.3 Surgical Planning

Radiopaque surgical guides (Fig. 2.3) allow the surgeon to plan the position of the crown or denture teeth (Ewers et al. 2010) and then use that information in the surgery to align the implant drills to the axis of the crown. The implant positions are planned using proprietary software, taking into account the crown position and occlusal load. Surgical guides can then be constructed using different rapid prototyping methodologies (e.g. stereolithography).

Surgical guides can be constructed that are bone, mucosa or tooth supported. Simulated surgery can be performed on the stereolithographic models with positioning of the implant directed by the surgical guide. This is followed by placement of the abutment on the model with construction of a provisional crown. Placing implants in the patient follows the same sequence, i.e. using the surgical guide to prepare the bone site for the implants, with placement of the abutment and provisional crown (Kamposiora et al. 2012). Other recent developments include virtual combining (or registering) optical impressions of the dentition, using CEREC scanning, with CBCT data (Ritter et al. 2012). This method avoids the radiation exposure to the patient that arises from them having to wear a template during a separate CBCT scanning procedure and is highly accurate.



**Fig. 2.3** A radiopaque guide allows the dentist to visualise the implant and its relation to vital structures when planning implant placement

The patient illustrated in Fig. 2.4 has missing upper central incisors and requested implant-borne replacements. A series of cone beam CT images of the anterior maxilla in coronal (Fig. 2.4a), sagittal (Fig. 2.4b) and axial views (Fig. 2.4c) illustrates the radiopaque surgical guide in situ. The bottom right part of the figure (Fig. 2.4d) shows a volume-rendered image. A denture was constructed for the patient, taking care that she was satisfied with the tooth position, and this was duplicated to produce a radiopaque acrylic surgical stent. There has been some bone loss of the anterior residual ridge.

### 2.3.1 Devices Used for Measuring Implant Stability

Dental implant stability can be assessed by two commercially available techniques: resonance frequency analysis (RFA, manufactured by Osstell ISQ) and damping capacity assessment (Periotest, manufactured by Medizintechnik Gulden, Germany). In the Periotest, a rod taps the implant over a few seconds, and the time during which the rod and implant are in contact is measured and converted into Periotest stability values. Zix et al. (2008) found that the Periotest was less precise and less reproducible than the Osstell device. Both techniques gave values which were correlated with the implant diameter, but it is not clear if this is because





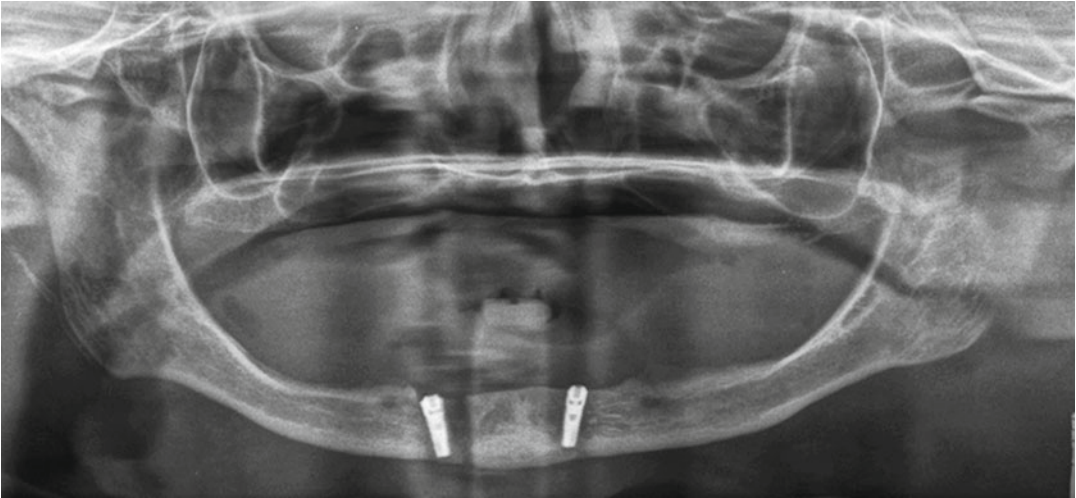
**Fig. 2.4** The cone beam CT image of the implant site taken with a radiopaque stent in place (a) Coronal, (b) sagittal, and (c) axial views. (d) Volume-rendered image

wider implants are more stable. Using resonance frequency analysis, Ohta et al. (2010) found no correlation between stability values recorded and implant diameter, using implants placed in pig cortical bone.

There is no gold standard method of assessing implant stability. The force needed to insert an implant (insertion torque) has been used, but to measure insertion torque precisely, dedicated devices are required. Degidi et al. (2010) found that there was no significant correlation between RFA values and insertion torque, signifying that they are measuring different bone parameters. In addition, surgeons underestimated implant stability as measured by RFA, which would indicate that an objective measure of implant stability is required if immediate loading is planned.

Ultrasound devices are used to determine bone density (Kaufman et al. 2007). Other authors (Mathieu et al. 2011) have investigated the use of quantitative ultrasound for the detection of implant stability and found that the method could detect an alteration of 1 mm in the contact length of bone and implant.

Figure 2.5 illustrates the placement of a right mandibular implant that lacked primary stability. The surgeon removed this implant and placed a second implant adjacent to the first. The mandible was weakened and subsequently fractured, which necessitated mandibular plating (Fig. 2.6). This unfortunate set of circumstances may have been avoided if the surgeon had been able to preoperatively assess the bone density of the operative site.



**Fig. 2.5** The implant placed in the right anterior mandible lacked primary stability



**Fig. 2.6** The dentist removed the loose right implant seen in Fig. 2.5, and drilled another bony region adjacent to the first implant recipient site. The mandible subsequently fractured and was plated

### 2.3.2 Optimal Size of Implants

Mathematical models have shown that an implant diameter of less than 3 mm is insufficient for sustained clinical success (Ojeda et al. 2011). The use of short implants of 10 mm length or less is controversial, but studies generally report failure rates comparable to that of normal length

implants. If short implants are used, the likelihood of nerve damage or other morbidity is reduced and costs are less, but despite this, the use of normal length implants with bone grafting techniques is preferred by some clinicians. These clinicians point to the insufficient follow-up period of short implants in mostly retrospective studies (less than 5 years), the small numbers of

study participants and the lack of information on potentially confounding clinical variables, e.g. bone quality. Despite this, the success of short implants may be due to recent improvements in their roughened surface design, combined with good primary stability at insertion (Annibali et al. 2012).

If a short implant (<10 mm in length) achieves osseointegration, there is evidence that it will be functional. A systematic review endorsed the use of 9.5-mm-long dental implants with an estimated survival rate of 98.6 % (95 % CI: 94.6–100 %) after 2 years (Tellemann et al. 2011). Many clinicians use the maximum implant length that can be achieved, based on laboratory tests and finite element analysis that have shown reduced stresses with longer implants. However, the stresses at the bone-implant interface have not been verified clinically or even what is an acceptable amount of stress at this point during function.

Providing a firm and stable implant in sufficient bone is key to a successful result. This can usually be achieved when the implant engages the thick cortical bone in the mandible, but in the maxillary molar region, the cortical bone is thin with fine cancellous bone. If the host site has a reduced bone density, a large proportion of the bone is easily damaged by placing an implant. Alghamdi et al. (2011) showed that under-preparing the width of the implant site in low-density bone produced good stability. By producing an undersized host site implant, this allowed improved initial implant stability but may be at the expense of crushing bone and causing necrosis when the wider implant was inserted. If an implant is loose at insertion, some surgeons use a wider implant, but this also may cause bone crushing and fracture of trabeculae. Seong et al. (2011) described using a bone cement filler placed around the loose implant to improve the initial stability. No soft tissue or bony necrosis was observed. The bone cement achieved biocompatibility because it was mainly composed of Portland cement (a mixture of tricalcium silicate, dicalcium silicate, tricalcium aluminate and calcium aluminoferrite minerals). Other constituents include calcium sulphate, carbon fibres and a dis-

persant (hydroxyethyl cellulose). Setting occurs when the cement comes in contact with water. Calcium sulphate is added to prevent a rapid set and to improve the strength of the set cement. Other additives to the bone cement such as antibiotic derivatives may prevent bacterial colonisation of the implant. Adding vancomycin-derivative antibiotics (i.e. vancomycin-PEG(3400)-acrylate) to bone cement reduces bacterial adherence but has a deleterious effect on the mechanical properties of the cement (Lawson et al. 2010). A further problem with antibiotic-loaded bone cements is that there is a sudden release of antibiotic from the surface in the early stages, but this release is not sustained.

Many surgeons provide preoperative systemic antibiotic prophylaxis for routine patients prior to implant insertion, but this is a controversial issue. A study by Gynther et al. (1998) did not show any significant reduction in post-operative infection rate or implant survival compared with those who received no antibiotics. Their regime involved giving 1 g of phenoxymethyl penicillin 1 h preoperatively and a further 1 g every 8 h for 10 days postoperatively. Esposito et al. (2010) found no significant difference in implant failure rate between those patients given prophylactic antibiotics and those given none. Their antibiotic prophylaxis regime involved giving orally 2 g amoxicillin 1 hour prior to implant placement. Antibiotics are entirely appropriate in those who are immunocompromised or those at risk of bisphosphonate-related osteonecrosis of the jaw (Termine et al. 2009). There is little scientific evidence for providing antibiotic prophylaxis in healthy patients with no medical complications.

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## 2.4 The Bone–Implant Interface

### 2.4.1 Platform Switching

The micro-gap between an implant and its matched abutment is easily colonised by bacteria, and the patient will find it difficult to maintain its cleanliness. This can give rise to periodontal disease and bone loss. In vitro studies have shown



that microorganisms can penetrate the abutment–implant interface (Quirynen et al. 1994). Once the alveolar bone has resorbed sufficiently, the bacteria at the micro-gap are no longer in contact with the bone and the rate of bone loss slows. “Platform switching” has been described as a method of placing the implant–abutment interface away from the surrounding alveolar bone by placing a narrower diameter abutment on top of the implant. The micro-gap is then placed away from the outer edge of the implant.

It is thought that platform switching may also reduce stress at the implant–bone interface. Studies using finite element analysis (Tabata et al. 2011) and photoelastic studies (Rossi et al. 2011) have shown a favourable stress distribution with this technique.

## 2.4.2 Implant Surface Modification

Exposure of rough plasma-sprayed coatings and threaded surfaces of implants contributes to plaque formation. They encourage the formation of a biofilm. The routine use of preoperative antibiotics for implant placement is controversial. Although some studies have reported improvements in implant survival (Laskin et al. 2000) with preoperative antibiotics, the improvement in failure rate is small (Sharaf et al. 2011). Despite the lack of evidence to support this practice, the routine use of preoperative antibiotic therapy in implant placement is widespread. There are risks of allergic reactions and bacterial resistance associated with the widespread use of antibiotics. Programmes to improve the patient’s

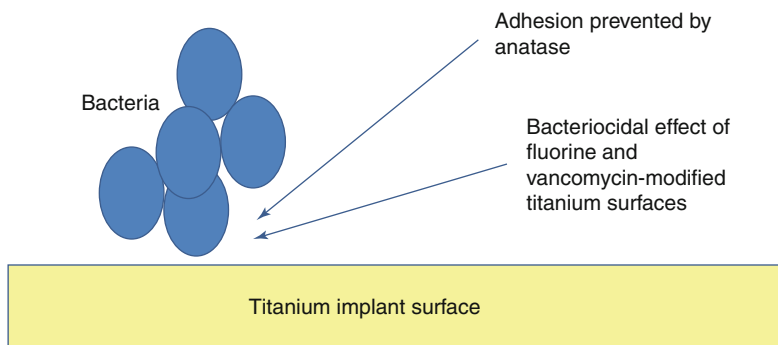
oral hygiene, combined with tobacco cessation, are more likely to be effective in preventing post-operative infections and implant loss, even in those patients with chronic periodontitis (Ellegaard et al. 1997).

Experimental approaches have involved modification of the implant surface with anatase, fluorine and vancomycin (Fig. 2.7), but the initial success has not yet resulted in randomised controlled trials to prove their efficacy.

The ideal implant protective coating would have an antibacterial action, encourage osseointegration and promote a perimucosal seal.

## 2.4.3 Preventing Bacterial Adherence

An in vivo study reported reduced bacterial adherence on TiN-coated implants compared with uncoated implants (Scarano et al. 2003). Twelve test and 12 control implants were tested by attaching them to acrylic appliances in each quadrant of the mouth in six patients. The surface roughness of both TiN-coated and titanium surfaces was similar. Similarly, an in vitro study has shown that the adhesion of *S. mutans* and *S. sanguis* to a TiN surface is reduced compared with polished titanium (Grössner-Schreiber et al. 2001). Deposition of a hard TiN coating is thought to alter the deposition of salivary pellicle proteins, making it more difficult for bacteria to colonise the implant surface. There is a general reduction in bacterial numbers rather than a reduction in the range of organisms affected (Grössner-Schreiber et al. 2009). This would make it a



**Fig. 2.7** Current experimental approaches to preventing bacterial adhesion and growth on implant surfaces

suitable coating for the transmucosal element of implants.

#### 2.4.4 Promoting Osseointegration

Incorporating bone morphogenetic protein-2 (BMP-2) growth factor into the surface coating of titanium alloy discs has been shown to induce new bone when they were implanted subcutaneously in rats (Liu et al. 2005). The biomimetic surface coating used in this study avoided high temperatures during manufacture (which would have destroyed the biological activity of the BMP-2). Bone formation was continuous for the duration of the experiment, which distinguished it from the action of surface-adsorbed BMP-2 where bone formation occurs in an early rapid burst. Further testing of the biomimetic coating is necessary to determine its shelf life and whether it will resist the shearing forces that occur during implant placement.

Threaded zirconia implants (surface etched with hydrofluoric acid) have been shown to osseointegrate as well as titanium implants (Gahlert et al. 2012). Zirconia has the advantage over titanium that it is tooth coloured, and bacterial adhesion and colonisation of the surface were found to be lower (Scarano et al. 2004).

## 2.5 Conclusion and Future Perspectives

If a patient does not have sufficient bone surrounding and supporting the implant, then it will fail. Therefore, the patient's bone quantity and quality is crucial in determining the likelihood of implant failure. The effect of genetic factors, systemic disease and environmental factors on implant success can all be analysed by their effect on the host bone. Despite this, there are few (if any) methods of analysis of the architecture of bone in vivo which have been shown to predict implant success.

Recent developments in 3D cone beam CT imaging allow the visualisation of important anatomical structures such as the maxillary sinus

or incisive canal. Cross-sectional imaging is essential to determine the adequacy of the width and height of the alveolar process. 3D imaging can also be combined with implant planning software. Future developments should see further technical developments associated with cone beam CT imaging for implants, e.g. improved soft tissue contrast and artefact reduction.

As well as the host bone volume and density, other crucial factors in implant success include the surgical skill of the operator and the nature of the implant surface. Both are important in encouraging early differentiation of mesenchymal stem cells to form osteoblasts and bone. Further research will show the merits (if any) of using various methods of stimulating bone formation, e.g. through coating the implant surface with osteogenic growth factors such as recombinant human bone morphogenetic protein-2.

## References

- Aglietta M, Siciliano VI, Zwahlen M, Brgger U, Pjetursson BE, Lang NP, Salvi GE (2009) A systematic review of the survival and complication rates of implant supported fixed dental prostheses with cantilever extensions after an observation period of at least 5 years. *Clin Oral Implants Res* 20(5): 441–451
- Alghamdi H, Anand PS, Anil S (2011) Undersized implant site preparation to enhance primary implant stability in poor bone density: a prospective clinical study. *J Oral Maxillofac Surg* 69:e506–e512
- Andreietelli M, Att W, Strub JR (2010) Prosthodontic complications with implant overdentures: a systematic literature review. *Int J Prosthodont* 23(3):195–203
- Annibali S, Cristalli MP, Dell'aquila D, Bignozzi I, La Monaca G, Pilloni A (2012) Short dental implants: a systematic review. *J Dent Res* 91:25–32
- Bell KL, Loveridge N, Jordan GR et al (2000) A novel mechanism for induction of increased cortical porosity in cases of intracapsular hip fracture. *Bone* 27:297–304
- Buser D, Weber HP, Brgger U, Blsiger C (1991) Tissue integration of one-stage ITI implants: 3-year results of a longitudinal study with Hollow-Cylinder and Hollow-Screw implants. *Int J Oral Maxillofac Implants* 6:405–12
- Degidi M, Dapriale G, Piattelli A (2010) Determination of primary stability: a comparison of the surgeon's perception and objective measurements. *Int J Oral Maxillofac Implants* 25:558–561

- Devlin H, Horner K (2007) A study to assess the relative influence of age and edentulousness upon mandibular bone mineral density in female subjects. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 104: 117–121
- Ellegaard B, Baelum V, Karring T (1997) Implant therapy in periodontally compromised patients. *Clin Oral Implants Res* 8:180–188
- Esposito M, Grusovin MG, Chew YS, Coulthard P, Worthington HV (2009) Interventions for replacing missing teeth: 1- versus 2-stage implant placement. *Cochrane Database Syst Rev* Issue 3. Art. no.: CD006698. doi: [10.1002/14651858.CD006698](https://doi.org/10.1002/14651858.CD006698.pub2). CD006698. pub2
- Esposito M, Cannizzaro G, Bozzoli P, Checchi L, Ferri V, Landriani S, Leone M, Todisco M, Torchio C, Testori T, Galli F, Felice P (2010) Effectiveness of prophylactic antibiotics at placement of dental implants: a pragmatic multicentre placebo-controlled randomised clinical trial. *Eur J Oral Implantol* 3:135–143
- Ewers R, Seemann R, Krennmair G, Schicho K, Kurdi AO, Kirsch A, Reichwein A (2010) Planning implants crown down – a systematic quality control for proof of concept. *J Oral Maxillofac Surg* 68(11):2868–2878
- Friberg B, Jemt T, Lekholm U (1991) Early failures in 4,641 consecutively placed Brånemark dental implants: a study from stage I surgery to the connection of completed prostheses. *Int J Oral Maxillofac Implants* 6:142–146
- Friberg B, Ekestubbe A, Mellström D, Sennerby L (2001) Brånemark implants and osteoporosis: a clinical exploratory study. *Clin Implant Dent Relat Res* 3:50–56
- Fuster-Torres MÁ, Peñarrocha-Diogo M, Peñarrocha-Oltra D, Peñarrocha-Diogo M (2011) Relationships between bone density values from cone beam computed tomography, maximum insertion torque, and resonance frequency analysis at implant placement: a pilot study. *Int J Oral Maxillofac Implants* 26: 1051–1056
- Gahlert M, Roehling S, Sprecher CM, Kniha H, Milz S, Bormann K (2012) In vivo performance of zirconia and titanium implants: a histomorphometric study in mini pig maxillae. *Clin Oral Implants Res* 23:281–286
- Gomes de Oliveira RC, Leles CR, Lindh C, Ribeiro-Rotta RF (2012) Bone tissue microarchitectural characteristics at dental implant sites. Part 1: identification of clinical-related parameters. *Clin Oral Implants Res* 23(8):981–986. doi: [10.1111/j.1600-0501.2011.02243.x](https://doi.org/10.1111/j.1600-0501.2011.02243.x)
- Grössner-Schreiber B, Griepentrog M, Haustein I, Müller WD, Lange KP, Briedigkeit H, Göbel UB (2001) Plaque formation on surface modified dental implants. An in vitro study. *Clin Oral Implants Res* 12: 543–551
- Grössner-Schreiber B, Teichmann J, Hannig M, Dörfer C, Wenderoth DF, Ott SJ (2009) Modified implant surfaces show different biofilm compositions under in vivo conditions. *Clin Oral Implants Res* 20:817–826
- Gynther GW, Köndell PA, Moberg LE, Heimdahl A (1998) Dental implant installation without antibiotic prophylaxis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 85:509–511
- Hutton JE, Heath MR, Chai JY et al (1995) Factors related to success and failure rates at 3 year follow up in a multicenter study of overdentures supported by Brånemark implants. *Int J Oral Maxillofac Implants* 10:33–42
- Jang HW, Kang JK, Lee K, Lee YS, Park PK (2011) A retrospective study on related factors affecting the survival rate of dental implants. *J Adv Prosthodont* 3:204–215
- Kacer CM, Dyer JD, Kraut RA (2010) Immediate loading of dental implants in the anterior and posterior mandible: a retrospective study of 120 cases. *J Oral Maxillofac Surg* 68:2861–2867
- Kamposiora P, Papavasiliou G, Madianos P (2012) Presentation of two cases of immediate restoration of implants in the esthetic region, using facilitate software and guides with stereolithographic model surgery prior to patient surgery. *J Prosthodont* 21:130–137
- Kaufman JJ, Luo G, Siffert RS (2007) A portable real-time ultrasonic bone densitometer. *Ultrasound Med Biol* 33:1445–1452
- Lambert FE, Weber HP, Susarla SM, Belser UC, Gallucci GO (2009) Descriptive analysis of implant and prosthodontic survival rates with fixed implant-supported rehabilitations in the edentulous maxilla. *J Periodontol* 80(8):1220–1230
- Laskin DM, Dent CD, Morris HF, Ochi S, Olson JW (2000) The influence of preoperative antibiotics on success of endosseous implants at 36 months. *Ann Periodontol* 5:166–174
- Lawson MC, Hoth KC, Deforest CA, Bowman CN, Anseth KS (2010) Inhibition of *Staphylococcus epidermidis* biofilms using polymerizable vancomycin derivatives. *Clin Orthop Relat Res* 468: 2081–2091
- Lee S, Gantes B, Riggs M, Crigger M (2007) Bone density assessments of dental implant sites: 3. Bone quality evaluation during osteotomy and implant placement. *Int J Oral Maxillofac Implants* 22:208–212
- Lekholm U (1992) The Brånemark implant technique: a standardized procedure under continuous development. In: Laney WR, Tolman DF (eds) *Tissue integration in oral, orthopedic and maxillofacial reconstruction*. Quintessence, Chicago, pp 194–199
- Lekholm U, Zarb GA (1985) Patient selection and preparation. In: Brånemark P-I, Zarb GA, Albrektsson T (eds) *Tissue-integrated prosthesis: osseointegration in clinical dentistry*. Quintessence, Chicago, pp 199–209
- Liao KY, Kan JY, Rungcharassaeng K, Lozada JL, Herford AS, Goodacre CJ (2010) Immediate loading of two freestanding implants retaining a mandibular overdenture: 1-year pilot prospective study. *Int J Oral Maxillofac Implants* 25:784–790
- Lin CL, Wang JC, Ramp LC, Liu PR (2008) Biomechanical response of implant systems placed in the maxillary posterior region under various conditions of

- angulation, bone density, and loading. *Int J Oral Maxillofac Implants* 23:57–64
- Liu Y, de Groot K, Hunziker EB (2005) BMP-2 liberated from biomimetic implant coatings induces and sustains direct ossification in an ectopic rat model. *Bone* 36:745–757
- Malo P, Nobre M, Lopes A (2011) The rehabilitation of completely edentulous maxillae with different degrees of resorption with four or more immediately loaded implants: a 5-year retrospective study and a new classification. *Eur J Oral Implantol* 4:227–243
- Mathieu V, Anagnostou F, Soffer E, Haiat G (2011) Numerical simulation of ultrasonic wave propagation for the evaluation of dental implant biomechanical stability. *J Acoust Soc Am* 129:4062–4072
- McAlarney ME, Stavropoulos DN (1996) Determination of cantilever length-anterior-posterior spread ratio assuming failure criteria to be the compromise of the prosthesis retaining screw-prosthesis joint. *Int J Oral Maxillofac Implants* 11(3):331–339
- Moy PK, Medina D, Shetty V, Aghaloo TL (2005) Dental implant failure rates and associated risk factors. *Int J Oral Maxillofac Implants* 20(4):569–577
- Nackaerts O, Maes F, Yan H, Couto Souza P, Pauwels R, Jacobs R (2011) Analysis of intensity variability in multislice and cone beam computed tomography. *Clin Oral Implants Res* 22:873–879
- Ohta K, Takechi M, Minami M, Shigeishi H, Hiraoka M, Nishimura M, Kamata N (2010) Influence of factors related to implant stability detected by wireless resonance frequency analysis device. *J Oral Rehabil* 37:131–137
- Ojeda J, Martínez-Reina J, García-Aznar JM, Domínguez J, Doblaré M (2011) Numerical simulation of bone remodelling around dental implants. *Proc Inst Mech Eng H* 225:897–906
- Osier JF (1991) Biomechanical load analysis of cantilevered implant systems. *J Oral Implantol* 17(1):40–47
- Quirynen M, Bollen CM, Eyssen H, van Steenberghe D (1994) Microbial penetration along the implant components of the Branemark System. An in vitro study. *Clin Oral Implants Res* 5:239–244
- Ritter L, Reiz SD, Rothamel D, Dreiseidler T, Karapetian V, Scheer M, Zöller JE (2012) Registration accuracy of three-dimensional surface and cone beam computed tomography data for virtual implant planning. *Clin Oral Implants Res* 23:447–452
- Roberts M, Yuan J, Graham J, Jacobs R, Devlin H (2011) Changes in mandibular cortical width measurements with age in men and women. *Osteoporos Int* 22:1915
- Roe P, Kan JY, Rungcharassaeng K, Lozada JL (2011) Immediate loading of unsplinted implants in the anterior mandible for overdentures: 3-year results. *Int J Oral Maxillofac Implants* 26:1296–1302
- Rossi F, Zavanelli AC, Zavanelli RA (2011) Photoelastic comparison of single tooth implant-abutment bone of platform switching vs conventional implant designs. *J Contemp Dent Pract* 12:124–130
- Scarano A, Piattelli M, Vrespa G, Caputi S, Piattelli A (2003) Bacterial adhesion on titanium nitride-coated and uncoated implants: an in vivo human study. *J Oral Implantol* 29:80–85
- Scarano A, Piattelli M, Caputi S, Favero GA, Piattelli A (2004) Bacterial adhesion on commercially pure titanium and zirconium oxide disks: an in vivo human study. *J Periodontol* 75:292–296
- Schliephake H, Neukam FW, Wichmann M (1997) Survival analysis of endosseous implants in bone grafts used for the treatment of severe alveolar ridge atrophy. *J Oral Maxillofac Surg* 55:1227–1234
- Seong WJ, Kim HC, Jeong S, DeVeau DL, Aparicio C, Li Y, Hodges JS (2011) Ex vivo mechanical properties of dental implant bone cement used to rescue initially unstable dental implants: a rabbit study. *Int J Oral Maxillofac Implants* 26:826–836
- Sharaf B, Jandali-Rifai M, Susarla SM, Dodson TB (2011) Do perioperative antibiotics decrease implant failure? *J Oral Maxillofac Surg* 69:2345–2350
- Tabata LF, Rocha EP, Barão VA, Assunção WG (2011) Platform switching: biomechanical evaluation using three-dimensional finite element analysis. *Int J Oral Maxillofac Implants* 26:482–491
- Telleman G, Raghoobar GM, Vissink A, den Hartog L, Huddleston Slater JJ, Meijer HJ (2011) A systematic review of the prognosis of short (<10 mm) dental implants placed in the partially edentulous patient. *J Clin Periodontol* 38:667–676
- Termine N, Panzarella V, Ciavarella D, Lo Muzio L, D'Angelo M, Sardella A, Compilato D, Campisi G (2009) Antibiotic prophylaxis in dentistry and oral surgery: use and misuse. *Int Dent J* 59:263–270
- Turkyilmaz I, Tözüm TF, Tumer C, Ozbek EN (2006) Assessment of correlation between computerized tomography values of the bone, and maximum torque and resonance frequency values at dental implant placement. *J Oral Rehabil* 33:881–888
- Weng D, Jacobson Z, Tarnow D, Hürzeler MB, Faehn O, Sanavi F, Barkvoll P, Stach RM (2003) A prospective multicenter clinical trial of 3i machined-surface implants: results after 6 years of follow-up. *Int J Oral Maxillofac Implants* 18(3):417–423
- Zix J, Hug S, Kessler-Liechti G, Mericske-Stern R (2008) Measurement of dental implant stability by resonance frequency analysis and damping capacity assessment: comparison of both techniques in a clinical trial. *Int J Oral Maxillofac Implants* 23:525–530

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3.1 Introduction: Craniofacial and Maxillofacial Implants and Why They Fail

Osseointegrated implants have assisted the craniofacial and maxillofacial patient tremendously. Whether it be for a facial prosthetic reconstruction or an intraoral prosthetic reconstruction, the advent of endosteal implants has enhanced the maxillofacial prosthodontist’s ability to reconstruct tissues that were lost to either cancer, trauma, or an acquired congenital defect. These restorations can improve the quality of life of patients and give patients the ability to speak, masticate, and swallow (Beumer et al. 2010). They allow the ability to restore the patient’s appearance so that they feel comfortable going out in society. However, the long-term stability of craniofacial or maxillofacial implants has been less favorable than that of the conventional dental implant. This chapter discusses the specific features of craniofacial and maxillofacial implants to elucidate the factors relevant to the success and long-term stability of implant osseointegration.

3.2 Extraoral Craniofacial Implants

Traditionally, extraoral craniofacial implants serve as a retentive mechanism for facial prostheses and avoid reliance on medical grade adhesive. The advantages of craniofacial implants are multifold: (1) ease and accuracy of prosthesis

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placement, (2) improved tissue response (decreased skin reactions to adhesives) and patient comfort, (3) improved skin/prosthesis juncture between the prosthesis and skin, (4) improved retention and stability, and (5) increased life span of the prosthesis (Beumer et al. 2010). Surgical planning and prosthesis design vary significantly and can accommodate anatomical differences among the craniofacial tissues to be restored.

### 3.2.1 Auricular Implants

Given the anatomy of the ear, implants are placed within the confines of the antihelix. This allows optimization of the esthetics of the restoration by masking the implants. Implants are also placed in the temporal bone superior to the mastoid air cells (Fig. 3.1a). Because the bone in this area is very thin, small implants are regularly used. Furthermore, placing more implants in a curvilinear relation allows the implants to stay within the confinements of the antihelix of the ear. The inferior third of the ear is often located over large mastoid air cells making the host bone in this area a poor recipient for implants (Fig. 3.1b).

Soft tissue around implants can become inflamed following implant placement, and in many cases, highly polished porcelain is placed on the abutments to aid in maintaining the health of the soft tissue in this area. Patients with auricular defects require implants to assist in retaining the prosthesis. Cyclical loading is not seen in these types of restorations. Hader clips on a bar splint the implants together and allow for adequate stress distribution (Fig. 3.1c, d). An acrylic substructure links the clips to the silicone prosthetic ear.

### 3.2.2 Orbital Implants

Orbital implants present with complex restorative options given the anatomy. The superior orbital rim is typically a good recipient and can often accommodate implants. The medial aspect of the superior orbital rim often contains the frontal sinus and will not allow for implant placement in this area (Fig. 3.2a, b). In the event of loss of vision in one eye, the depth perception is less

optimal, and hence, using magnetic retention of the prosthesis allows patients to place the prosthesis more easily. In addition, the use of magnets allows for less axial force to be placed on the implants (Fig. 3.2c, d).

### 3.2.3 Nasal Implants

In nasal prosthetic reconstruction, dental implants may be placed in the floor of the nasal cavity. Placing implants in the glabella presents difficulty given the implant angulation and its proximity to the frontal sinus. Instead, the maxilla often has great vascularity and allows for standard maxillary osseointegration. Particular attention must be employed to avoid trauma to the apices of the natural teeth if they are present (Fig. 3.3a). Usually implants must be placed in the premaxillary segment at about a 45° angle due to the long axis of the adjacent teeth. The typical substructure consists of a bar with Hader clips (Fig. 3.3b). These implants are restored with an acrylic substructure linking to the implant bar (Fig. 3.3c).

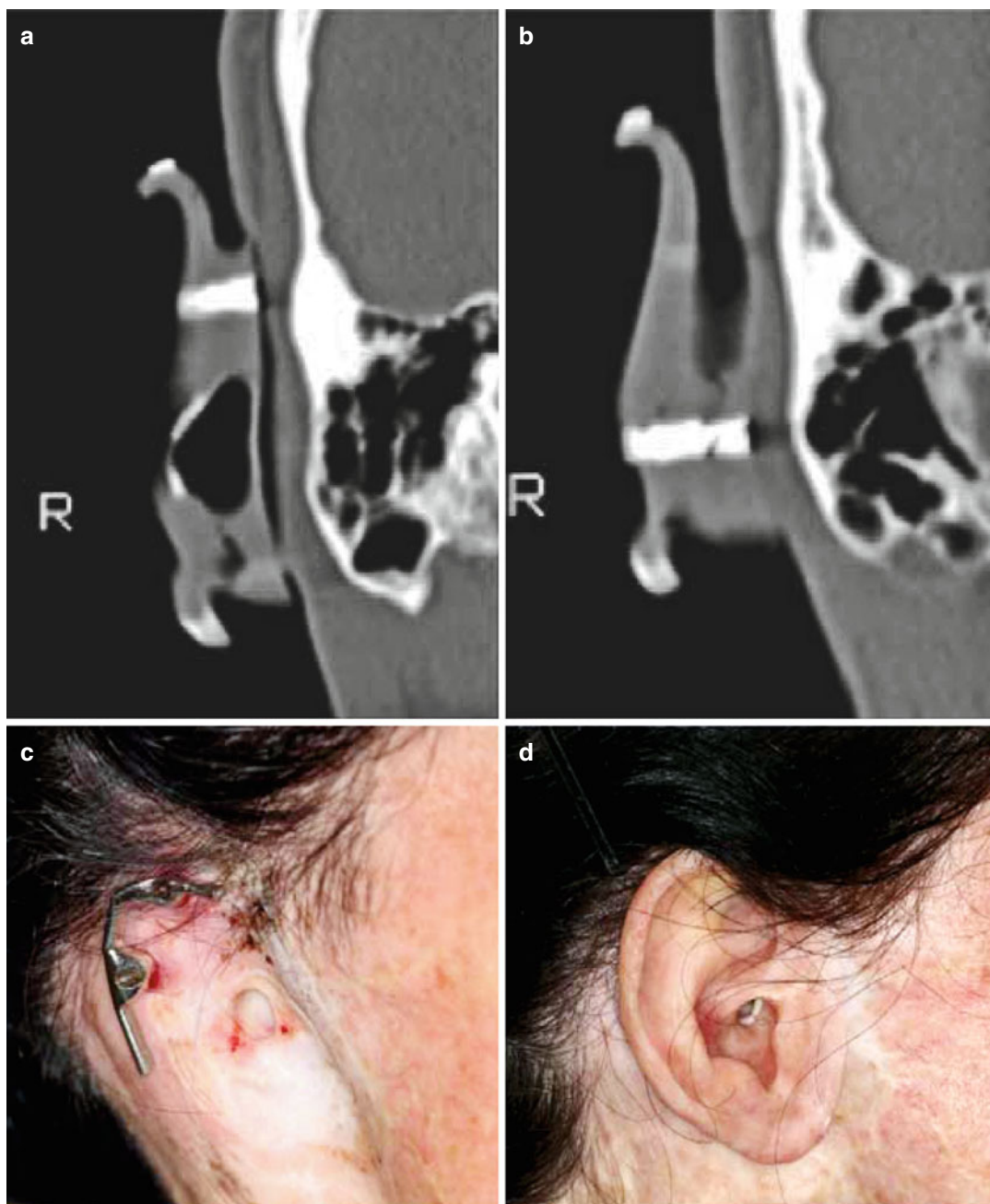
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## 3.3 The Long-Term Stability of Craniofacial Implants

### 3.3.1 Poor Implant Survival in Orbital Bone

In a retrospective review of 207 craniofacial implants placed in 72 patients, the overall survival rate for uncovered craniofacial implants was 80 %, which was significantly lower than that of the conventional dental implant. The detailed evaluation revealed that the cumulative 6-year survival rate for auricular, piriform/nasal, and orbital implants varied and was found to be 92, 87, and 59 %, respectively (Roumanas et al. 2002). Another study reported similar findings in their craniofacial prostheses patient population, i.e., that the survival of total implants in auricular, nasal, and orbital in congenital, trauma, and oncologic patients was 94.1, 88.9, and 80.8 %, respectively (Visser et al. 2008). Furthermore, in a study involving

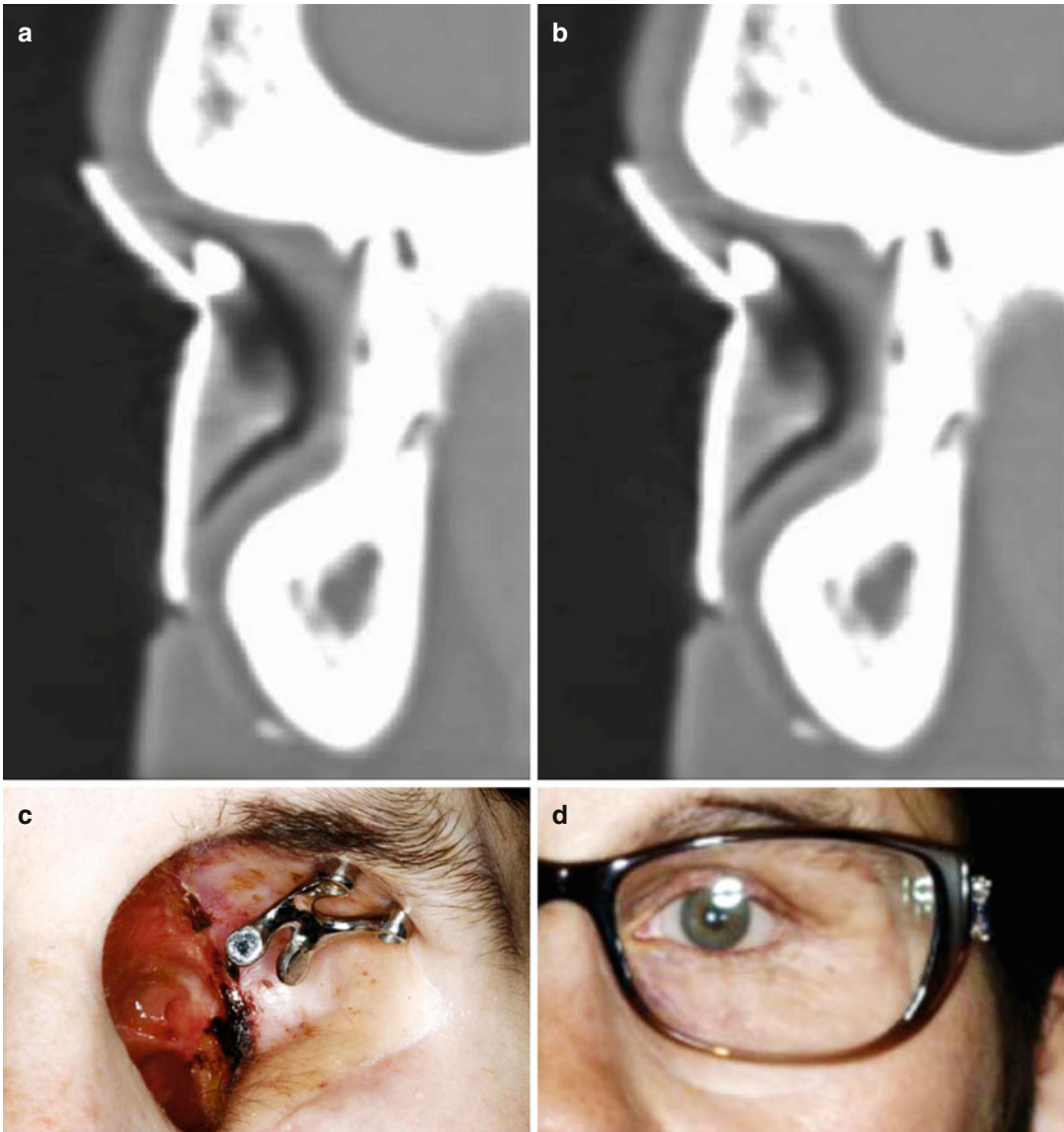




**Fig. 3.1** (a) Superior antihelix with guide. (b) Inferior antihelix with guide. (c) Hader bar. (d) Auricular prosthesis

153 implants placed to retain 44 orbital prostheses and followed for a mean period of 52.6 months, the overall integration survival rate was 73.2 % (Toljanic et al. 2005). From these studies, while craniofacial implants may offer significant benefits to patients, orbital bone presents a disadvantageous site for implant

treatment, and the long-term stability of orbital implants can be unpredictable. No obvious causes to explain the decreased orbital implant survival were found among factors such as radiation, hyperbaric oxygen therapy, or implant location within the orbital bone (Toljanic et al. 2005).

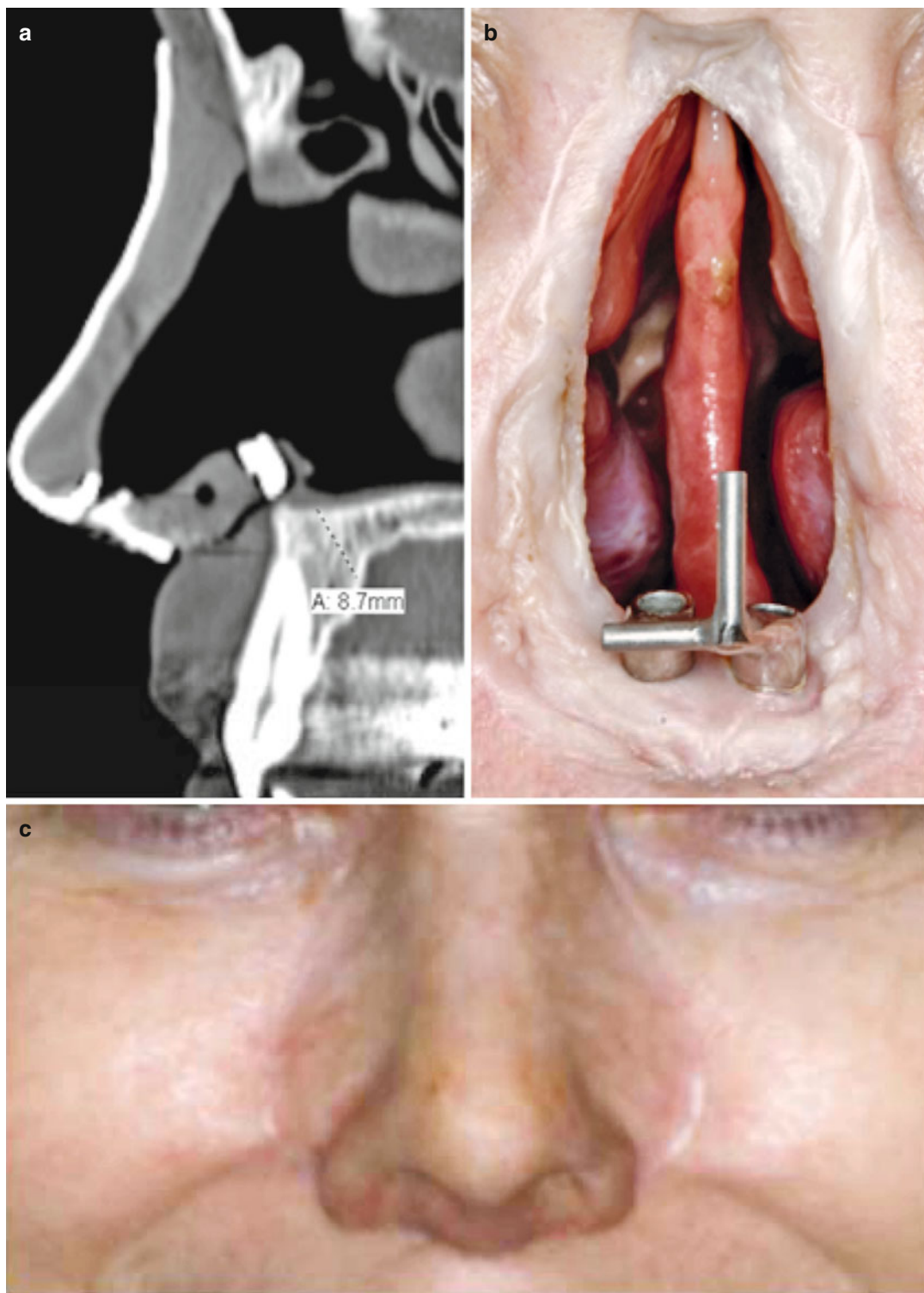


**Fig. 3.2** (a) Medial orbit with guide. (b) Lateral orbit with guide. (c) Lateral orbit with magnet attachment. (d) Orbital prosthesis

### 3.3.2 Effect of Radiation Therapy (XRT) on Craniofacial Implants

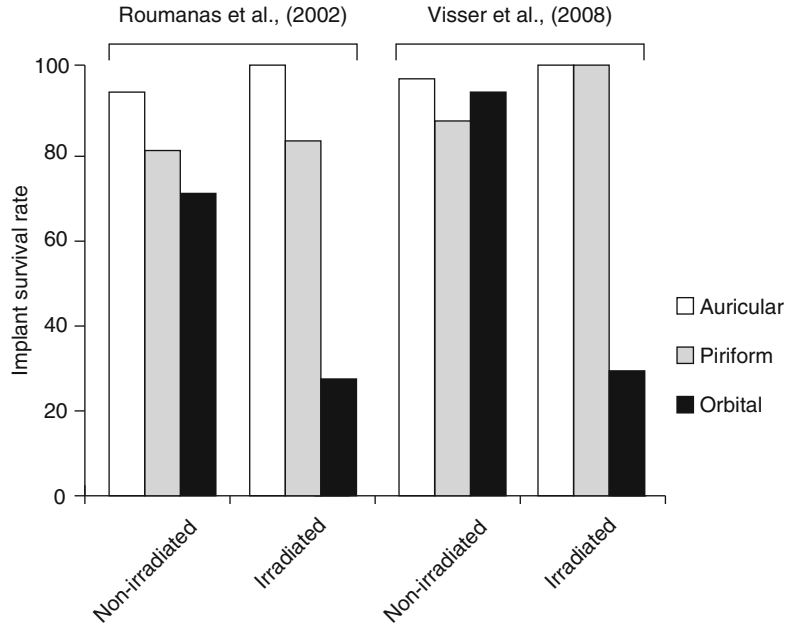
In a study of craniofacial prostheses retained by implants and adhesive in 10 patients, 5 patients had prostheses retained with implants utilizing a total of 14 implants, and 2 had failed that were placed in irradiated areas (Pekkan et al. 2011). In another study, implants placed in nonirradiated tissues and irradiated tissues were evaluated. In

nonirradiated tissues, survival rates for auricular, piriform, and orbital were 94, 80, and 70 %, respectively, with overall survival rate of 85 %. Survival rates in irradiated tissues for auricular, piriform, and orbital were 100, 83, and 27 %, respectively, with overall survival rate of 52 %. Limited numbers of orbital implants in patients were noted (Roumanas et al. 2002). Others reported in nonirradiated fields of the ear, nose, and orbit as 96, 87.5, and 94.1 %, respectively,



**Fig. 3.3** (a) Guide over central incisor. (b) Hader bar. (c) Restored nose

**Fig. 3.4** Craniofacial implant survival rate of auricular, piriform, and orbital prostheses reported by two independent studies



with overall survival rate of 95.2 %. Implants in irradiated bone were reported as placement pre-irradiation and postirradiation. Survival of implant placement postirradiation of auricular, nasal, and orbital bone was 100, 100, and 28.6 %, respectively. Implant placement survival with pre-irradiation of the auricular, nasal, and orbital bone was 81.8, 83.3, and 79.3 %, respectively (Visser et al. 2008).

These studies indicated that reduction of implant survival in irradiated tissues was rather limited to orbital bone (Fig. 3.4). In particular, orbital implants placed after XRT showed a significantly decreased survival, whereas the orbital implant placed before the radiation therapy sustained their survival albeit at a lower rate than those placed in other craniofacial bones. Case reports describing the failure of orbital bone implants after XRT began to emerge in the 1990s. An increased loss of implants with time after irradiation was noted (Granström et al. 1993).

### 3.3.3 Why Do Orbital Implants Fail?

To date, the cause of the selective reduction in the survival of orbital implants, particularly after XRT, has not been elucidated.

The human orbit is composed of the frontal, maxilla, zygomatic, and lacrimal bones. The orbital plate of the frontal bone occupies the superior margin where orbital implants are placed. This bone is a dense cortical bone. This location is also adjacent to the frontal sinus, which limits the implant length and direction.

Craniofacial implants are shorter than dental implants; typically these implants are about 3–4 mm in length. Craniofacial implants are also different from intraoral implants in that the implant surfaces of currently available craniofacial implants are untreated. Many of these implants have collars on the neck of the implant to prevent overseating during placement. Too deep placement would create damage to the underlying dura mater. The short length may partially explain why survival rates are less than that of intraoral dental implants.

Furthermore, the biomechanics of facial prostheses are different from the cyclic loading that intraoral implants undergo. However, implants placed in orbital bone are often subjected to off axial loading with loads applied perpendicular to the implants. These mechanical and anatomical issues may contribute to the loss of orbital implants.



### 3.3.4 Osseointegration of Craniofacial Implants

Anatomically, craniofacial bones are composed of relatively thick cortical bone and undeveloped trabecular bone. The initial implant stability may be established by the mechanical interaction between implant threads and cortical bone. It is believed that craniofacial implants may largely depend on this mechanical fixation. The orbital implants placed in the thin cortical bone may lack this initial fixation.

Bone remodeling is believed to be higher in trabecular bone than cortical bone, and thus, the biological establishment of osseointegration should be active with trabecular bone. In a preclinical animal study, implants were placed in the frontal calvarial region of nine adult pigs, and it was found that the bone-implant contact reached approximately 31 % at 2 weeks, 39 % after 4 weeks, and 51 % at 8 weeks (Petrovic et al. 2007). Implants placed in craniofacial bones should achieve osseointegration. However, the small trabecular bone compartment in craniofacial bones may be less adaptive for biological implant fixation. It is conceivable that radiation therapy reduces the viability of cells in the trabecular space. This may further impair the establishment of biological osseointegration involving bone remodeling.

It is tempting to speculate that osseointegration of craniofacial implants may highly depend on the mechanical fixation with cortical bone, while the *de novo* osseointegration in the trabecular space may not be effectively established. Although the rate of cortical bone remodeling may be slow, once the bone resorption is initiated, the loss of mechanical fixation may occur.

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## 3.4 Survival of Intraoral Maxillofacial Implants

Dental implants have been used to retain maxillofacial prostheses such as maxillary obturators. Depending on the configuration of implant placement, size of defect, number of implants, size of implants, and interocclusal space, splinted substructures or attachments are recommended. Splinting implants may allow for more even strain distribution on loading (Yilmaz et al. 2011).

It is important to note that these types of maxillofacial implants are placed in alveolar bone of the maxilla and mandible when there is ample bone. A relatively poor overall survival rate of implants was found at 69.2 %, with 63.6 % for the irradiated group and 82.6 % for the nonirradiated group (Roumanas et al. 1997). The majority of implant failures occurred in the maxilla. This may be partly due to unfavorable implant loading, e.g., a cantilever mechanical loading from a maxillary obturator, which may have a further disadvantageous effect. The maxillary implant survival was further decreased by XRT.

In another study, 446 implants were placed in the maxilla or mandible of cancer patients. In this study, they found that if implants are to fail in irradiated tissues, they will typically fail within the first 6 months. In this study, they found implants had an 84 % survival if the tissues received less than 50 Gy and 71 % if irradiated with greater than 50 Gy. More failures occurred in osseocutaneous grafts in the oral cavity (Visch et al. 2002).

### 3.4.1 Effect of XRT on Intraoral Maxillofacial Implant

A review of 11 animal studies and 16 human clinical studies assessing craniofacial and dental implant survival concluded that the risk of implant failure was greater in irradiated than nonirradiated bone (Ihde et al. 2009). In a systematic review of the literature, an evaluation of the effect of the dose and timing of XRT on implant failure was evaluated (Colella et al. 2007). In this systematic review, the implant failure rate was lower for the mandible (4.4 %) in comparison to the maxilla (17.5 %). The failure of maxillary implants placed after irradiation was significantly increased by 4.63 times when compared with postirradiation mandibular implants.

In a study where implants were placed in irradiated dog mandibles, it was found that loss of implants was radiation dose dependent. At the level of 40 Gy, the implants had 100 % survival; however, at 50 Gy, the implant survival decreased to 20 %, and at 60 Gy, all implants failed (Asikainen et al. 1998). An experimental animal study using minipigs showed the initial implant

stability was not affected by irradiation using resonance frequency analysis (RFA) to measure the implant stability quotient (ISQ). However, as time increased to week 8, 16, and 24, the ISQ was less than the control of healthy bone (Verdonck et al. 2008). In this study, pig maxilla and mandible received a total radiation dose of 24 Gy, and ISQ values were less in the mandible than the maxilla.

XRT has been shown to cause osteoradionecrosis, particularly in the mandible. While the cause of osteoradionecrosis has not been fully understood, two possible mechanisms have been postulated: (1) a radiation-induced obliteration of the vascular network in bone results in hypoxia or (2) a radiation-induced fibrosis in the bone marrow decreases the mesenchymal stem cell population. The fibrosis process is a multifactorial process involving cytokines, chemokines, angiogenic factors, growth factors, peroxisome proliferator-activated receptors, acute phase proteins, caspases, and components of the renin-angiotensin-aldosterone system (Wynn 2008). In this complex regulatory process, the mesenchymal stem cell population is decreased.

Following the hypoxic hypothesis, the use of hyperbaric oxygen (HBO) therapy has been proposed. In an *in vivo* study using 12 rabbits, a single dose of 15 Gy was administered to one hind leg, and the other hind leg served as the control. Titanium implants were placed into the femur and tibia immediately after irradiation. Six of the rabbits received HBO after implant placement. Histomorphometric analyses revealed that irradiation reduced the capacity for osseointegration of titanium implants, whereas HBO treatment appeared to improve bone-to-implant contact (Johnsson et al. 1999). If HBO is advantageous, then this protocol would support the hypoxia theory.

In order to elucidate the mechanism of HBO-assisted improvement in implant osseointegration, a qualitative study evaluating the trabecular bone regeneration in the osteotomy wound without implant placement in irradiated and nonirradiated rabbit femurs was studied. Unexpectedly, a large variation in the bone-forming capacity was noted. Qualitatively, histological

inflammation, fibrosis, and bone resorption were evident in the irradiated bone; however, the effect of HBO was not demonstrated (Johnsson et al. 2000). These mixed observations may question the validity of the hypoxia hypothesis of the mechanism of radiation-induced bone damages. In this study, the beneficial effects of HBO were not shown. The mechanism of irradiation-induced loss of implant osseointegration may be due to hypoxia, marrow fibrosis or both.

### **3.4.2 Implant Placement Before Tumor Ablation Surgery and XRT**

In a systematic review looking at the temporal relationship of implant placement, 41 studies were evaluated that fitted the inclusion criteria examining the survival of primary osseointegrated dental implants in head and neck oncology patients. This review examined advantages and disadvantages of pre-cancer dental implantation and post-cancer implant placement. Pre-cancer treatment allows for a decreased time to restoration and can limit the surgical options if the implants are placed perioperatively. Implants that are placed post-cancer treatment allow more time for planning and can avoid the adverse biological consequences of radiation therapy (Barber et al. 2011).

The pre-placed implants may receive a significant dose of radiation. If the primary tumor bed is in the area of the implant, backscatter of radiation to the bone juxtaposing the implant can be extensive within 1–2 mm of the implant body. There are reports of an increase in the radiation dose to bone near the titanium implant of up to 15 % due to the effect of backscattered radiation (Mian et al. 1987).

The placement of implants at the time of tumor resection can be advantageous by decreasing the number of surgical procedures and decreasing the amount of time taken for restoration. Placing implants at the same time as tumor resection surgery can present difficulties given the behavior of the tumor. This can create a lack of time to appropriately



obtain preoperative diagnostic information. If post-tumor ablation radiotherapy is given, the patient's implants may receive less radiation than primary radiation treatment. Radiation may damage the bone tissue near the implant. Backscatter of radiation due to the metal at and above the level of the gingivae can increase the dose by approximately 20 % (Farman et al. 1985).

In an animal study, which allowed 3 weeks for osseointegration of implants in dog mandibles, the bone was subjected to a dose equivalence of 50 Gy, delivered in 4 fractions during a 2-week period to evaluate the effects. Scanning electron microscopy was used to image the background electron density of bone, soft tissue, and implant. A histomorphometry calculation was performed on the irradiated tissues which showed approximately a 20 % decrease in bone-to-implant contact on machined surfaces and a modest 10 % decrease on plasma sprayed implants as compared to nonirradiated controls (Weinlaender et al. 2006).

A systematic review looking at the survival of implants pre-radiotherapy and post-radiotherapy suggested that failures in implants placed postirradiation were 3.2 % and those placed pre-irradiation therapy were 5.4 %, which was not statistically significant. No failures were noted in patients receiving less than 45 Gy; if failures occurred, it was at values greater than 45 Gy (Colella et al. 2007).

In one study (Schoen et al. 2001), 26 patients had received craniofacial implants in the auricular and orbital region, 12 of whom received implants at the time of tumor ablation, and 7 patients were treated with radiation therapy after surgery (mean 65 Gy). Fourteen patients received implants after the tumor surgery (5 patients received 54.4 Gy before implant placement). In the irradiated group, five implants were lost equating to an 87.8 % survival. No implants placed during or after tumor surgery were lost in patients who did not undergo radiation treatment (Schoen et al. 2001). Therefore, the outcome of placement of implants simultaneous with tumor ablation surgery or after tumor ablation may be more predictable when radiation therapy is not used.

### 3.4.3 Implants Placed Following Mandibular or Maxillary Reconstruction

The microscurgically reanastomosed fibula flap proves to be a suitable graft for the upper and lower jaw, allowing for endosseous implants to be placed. One study examined peri-implant bone resorption with fibula reconstruction and found that this was acceptable (Gbara et al. 2007). In one study, 128 implants were placed into the fibular graft with the result that 93 had pocket-probing depths of 2–3 mm; 20 implants had pocket depths of 4–6 mm and 4 implants had greater than 7 mm pockets. It was concluded that implants were a viable option when restoring the fibular-grafted bone (Gbara et al. 2007).

Implants placed in the fibula prior to grafting into the oral cavity have been studied in limited numbers, but they have been generally successful. In this protocol, implants are placed into the fibula prior to placing the fibular graft in the oral cavity and then are immediately loaded. In the limited cases reported, immediate loading of dental implants following this protocol showed survival rates of 100 and 93.3 % (Chiapasco and Gatti 2004).

Fibular flaps are often irradiated to cure microscopic disease. A study evaluated 44 patients in which 22 patients received tumoricidal doses of radiation therapy (>60 Gy). For the patients who received radiation, 20 preoperative and 10 postoperative HBO treatments were given. Patients were followed up for a mean of 41 months and no difference in survival was noted between implants placed in irradiated and non-irradiated fibular free flaps. The survival of implants placed in fibular flaps was 82.4 % and the survival rate in the native mandible on the unresected side was 88 %. If failures occurred, they were within the first 6 months after implant placement. The cumulative survival rate of implants was 91.9 % after a mean interval of 41 months. No difference in survival was observed between implants placed in the fibular grafts versus the native mandible (Salinas et al. 2010).

Implants placed in grafted bone exhibit unexpectedly good versatility and once

osseointegrated, they play an important role in stability, support, and retention of a prosthesis. However, a free flap tissue transfer can present with difficulties. For example, soft tissue management can be difficult given the skin associated with the free flap donor tissue is different from the oral mucosa. A skin paddle can present with hyperplastic tissue juxtaposing the implant.

### Conclusions

These studies indicate that there is an inherent decrease in survival rates in the subset of craniofacial and maxillofacial implants placed in the reconstruction of patients with cancer. However, the quality-of-life assessment studies found a beneficial functional and quality-of-life outcome. In one study, 28 rehabilitated patients restored from 1988 to 1999 with a total of 134 total implants received a questionnaire. It was found that 85.7 % of patients experienced no significant problems in various daily social activities, including dining in public. Therefore, oral rehabilitation using functional jaw reconstruction can reach a satisfactory level of esthetics, function, and psychosocial well-being of patients, thus improving their quality of life (Leung and Cheung 2003).

This review of craniofacial and intraoral implants further identified unique features highly relevant to the long-term stability of implant treatment. For example, orbital (frontal bone) and maxillary alveolar bone are repeatedly associated with a decreased implant survival. XRT appears to worsen implant survival at higher intensity levels.

### References

- Asikainen P, Klemett IE, Kotilainen R, Vuillemin T, Sutter F, Voipio HM, Kullaa A (1998) Osseointegration of dental implants in bone irradiated with 40, 50 or 60 Gy doses. An experimental study with beagle dogs. *Clin Oral Implants Res* 9:20–25
- Barber AJ, Butterworth CJ, Rogers SN (2011) Systematic review of primary osseointegrated dental implants in head and neck oncology. *Br J Oral Maxillofac Surg* 49:29–36
- Beumer J, Reisberg DJ, Marunick MT, Powers J, Kiatamnuay S, van Oort R, Zhao YM, Wu G, Eversole LR, Cherrick HM et al (2010) Rehabilitation of facial defects. In: Beumer J, Marunick MT, Esposito SJ (eds) *Maxillofacial rehabilitation*. Quintessence Publishing Co, Inc, Chicago
- Chiapasco M, Gatti C (2004) Immediate loading of dental implants placed in revascularized fibula free flaps: a clinical report on 2 consecutive patients. *Int J Oral Maxillofac Implants* 19:906–912
- Colella G, Cannavale R, Pentenero M, Gandolfo S (2007) Oral implants in radiated patients: a systematic review. *Int J Oral Maxillofac Implants* 22:616–622
- Farman AG, Sharma S, George DI, Wilson D, Dodd D, Figa R, Haskell B (1985) Backscattering from dental restorations and splint materials during therapeutic radiation. *Radiology* 156:523–526
- Gbara A, Darwich K, Li L, Schmelzle R, Blake F (2007) Long-term results of jaw reconstruction with microsurgical fibula grafts and dental implants. *J Oral Maxillofac Surg* 65:1005–1009
- Granström G, Tjellström A, Brånemark PI, Fornander J (1993) Bone-anchored reconstruction of the irradiated head and neck cancer patient. *Otolaryngol Head Neck Surg* 108:334–343
- Ihde S, Kopp S, Gundlach K, Konstantinovi VS (2009) Effects of radiation therapy on craniofacial and dental implants: a review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 107:56–65
- Johnsson AA, Sawaii T, Jacobsson M, Granström G, Turesson I (1999) A histomorphometric study of bone reactions to titanium implants in irradiated bone and the effect of hyperbaric oxygen treatment. *Int J Oral Maxillofac Implants* 14:699–706
- Johnsson AA, Jacobsson M, Granström G, Johansson CB, Strid K, Turesson I (2000) A microradiographic investigation of cancellous bone healing after irradiation and hyperbaric oxygenation: a rabbit study. *Int J Radiat Oncol Biol Phys* 48:555–563
- Leung AC, Cheung LK (2003) Dental implants in reconstructed jaws: patients' evaluation of functional and quality-of-life outcomes. *Int J Oral Maxillofac Implants* 18:127–134
- Mian TA, Van Putten MCJ, Kramer DC, Jacob RF, Boyer AL (1987) Backscatter radiation at bone-titanium interface from high-energy X and gamma rays. *Int J Radiat Oncol Biol Phys* 13:1943–1947
- Pekkan G, Tuna SH, Oghan F (2011) Extraoral prostheses using extraoral implants. *Int J Oral Maxillofac Surg* 40:378–383
- Petrovic L, Schlegel KA, Wiltfang J, Neukam FW, Rupprecht S (2007) Preclinical animal study and clinical trial of modified extraoral craniofacial implants. *J Plast Reconstr Aesthet Surg* 60:615–621

- Roumanas ED, Nishimura RD, Davis BK, Beumer J 3rd (1997) Clinical evaluation of implants retaining edentulous maxillary obturator prostheses. *J Prosthet Dent* 77:184–190
- Roumanas ED, Freymiller EG, Chang TL, Aghaloo T, Beumer J 3rd (2002) Implant-retained prostheses for facial defects: an up to 14-year follow-up report on the survival rates of implants at UCLA. *Int J Prosthodont* 15:325–332
- Salinas TJ, Desa VP, Katsnelson A, Miloro M (2010) Clinical evaluation of implants in radiated fibula flaps. *J Oral Maxillofac Surg* 68:524–529.20
- Schoen PJ, Raghoobar GM, van Oort RP, Reintsema H, van der Laan BF, Burlage FR, Roodenburg JL, Vissink A (2001) Treatment outcome of bone-anchored craniofacial prostheses after tumor surgery. *Cancer* 92:3045–3050
- Toljanic JA, Eckert SE, Roumanas E, Beumer J, Huryn JM, Zlotolow IM, Reisberg DJ, Habakuk SW, Wright RF, Rubenstein JE et al (2005) Osseointegrated craniofacial implants in the rehabilitation of orbital defects: an update of a retrospective experience in the United States. *J Prosthet Dent* 94:177–182
- Verdonck HW, Meijer GJ, Laurin T, Nieman FH, Stoll C, Riediger D, Stoelinga PJ, de Baat C (2008) Implant stability during osseointegration in irradiated and non-irradiated minipig alveolar bone: an experimental study. *Clin Oral Implants Res* 19:201–206
- Visch LL, van Waas MA, Schmitz PI, Levendag PC (2002) A clinical evaluation of implants in irradiated oral cancer patients. *J Dent Res* 81:856–859
- Visser A, Raghoobar GM, van Oort RP, Vissink A (2008) Fate of implant-retained craniofacial prostheses: life span and aftercare. *Int J Oral Maxillofac Implants* 23:89–98
- Weinlaender M, Beumer J 3rd, Kenney EB, Lekovic V, Holmes R, Moy PK, Plenck HJ (2006) Histomorphometric and fluorescence microscopic evaluation of interfacial bone healing around 3 different dental implants before and after radiation therapy. *Int J Oral Maxillofac Implants* 21:212–224
- Wynn TA (2008) Cellular and molecular mechanisms of fibrosis. *J Pathol* 214:199–210
- Yilmaz B, Seidt JD, McGlumphy EA, Clelland NL (2011) Comparison of strains for splinted and nonsplinted screw-retained prostheses on short implants. *Int J Oral Maxillofac Implants* 26(6):1176–1182

# Genetic Background of Implant Failure

# 4

Ichiro Nishimura

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## 4.1 Introduction: Cluster Failure

Contemporary dental implant therapy enjoys the highly predictable outcome of osseointegration, rapidly establishing the intimate connection between bone tissue and the surface of the endosseous implant fixture. Osseointegration can occur with an implant surface exhibiting various surface chemistries: i.e. commercially pure titanium, titanium alloys or crystalline/amorphous calcium phosphate and surface structures with isotropic turned or anisotropic micro- to nano-topography (Attard and Zarb 2005; Balshe et al. 2009; Cooper 2000; Mendonca et al. 2008; Stanford 2007). From a number of clinical outcome studies, an osseointegration-based implant is considered a safe and efficient treatment option in dentistry.

Dental practitioners have, however, experienced implant failure. It is widely accepted that implant failure within 1 year from the surgical placement of implant fixture may be due to the failed achievement of osseointegration. On the contrary, implant failure after the prostheses are in place may be due to the failure in maintaining the once-established osseointegration. Esposito et al. (1998) compiled the published data and reported an approximately equal rate of implant failures during early and late stages (Esposito et al. 1998). However, etiological and pathological factors contributing to the implant failures in the early and late stages may be distinct and thus require further elucidation.

In the multicentre clinical trials and longitudinal cohort studies, the rate of implant failure has been calculated by the number of implant fixtures lost at a given time over the total number of implants placed. This method assumes each implant as an independent variable. It is known, however, that osseointegration failure may occur in a “cluster,” i.e. that the failure of multiple implants tends to occur in a certain patient. Friberg et al. (1997) reported that 5 out of 103 patients accounted for more than 85 % of the fixture losses (Friberg et al. 1997). In their prospective three-centre study, three patients lost all six implants and two patients were found having 2–3 mobile implant fixtures. This phenomenon, termed “cluster failure,” has been commonly recognized (Jemt and Hager 2006; Schwartz-Arad et al. 2008).

The clustered nature of implant failure prompted detailed statistical analyses addressing the potential etiopathological factors contributing to the interdependency between failed implants being placed in the same patient. Chuang and colleagues analyzed the implant failure in a cohort of 677 patients who had 2,349 implants placed (Chuang et al. 2002a, b). The adjusted multivariate modeling using the Cox proportional hazards model identified smoking, immediate implant placement after tooth extraction and the one-stage protocol as risk factors; however, they did not demonstrate the interdependency of implants within the same patients as a significant risk.

Subsequently, when the same cohort was re-evaluated by a different statistical method, those risk factors previously associated with implant failure were found to vary significantly among different patients (Chuang 2005). In other words, the cluster nature of implant failure can occur in patients who do not smoke or received rather conservative implant surgery. These habitual or surgical variations contributing to the seemingly disadvantageous environment, such as smoking, may not be the primary factor to explain the clustered implant failure.

Furthermore, multiple implants failures occur simultaneously within the same patient, although the timing of failure varies among patients. The

clustered nature of implant failure cannot be explained only by the implant-associated variables, but rather indicates that the patient-related variables may need to be considered. In this chapter, the potential role of genetic variations is discussed.

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## 4.2 Gene and Environment Interaction: On Common Dental Diseases

“Almost all diseases result from a complex interaction between an individual’s genetic make-up and environmental agents,” stated by the National Institute of Environmental Health Sciences, the US National Institutes of Health (<http://www.niehs.nih.gov/health/topics/science/gene-env/index.cfm>). The involvement of specific gene mutation has been well established in rare but severe inheritable diseases. Syndromes involving craniosynostosis such as Apert syndrome, Pfeiffer syndrome, Crouzon syndrome and Beare-Stevenson syndrome are caused by mutations in the fibroblast growth factor receptor (FGFR)-related genes (Marie et al. 2005; Melville et al. 2010). Each genetic mutation activates the function of FGFR in the cranial suture without the putative ligands, leading to premature suture tissue ossification. FGFR gene mutations rarely occur but significantly affect the patients’ cranial development without much of an environmental contribution.

On the contrary, common diseases are influenced more by environmental factors. Dental caries, one of the most frequent common diseases, is believed to occur in the “cariogenic” environment (Kleinberg 2002; Paes Leme et al. 2006). *Streptococcus mutans* has been identified as causing dental caries. Gnotobiotic animals inoculated only with *S. mutans* demonstrated a good correlation with the disease initiation (Bowen and Koo 2011; Smith and Spatafora 2012). Fluoride exposure and diet are other contributing environmental factors related to dental caries. The sugar consumption of 19 lb/person/year in 1850 compared to 90 lb/person/year in 1900 has explained why dental caries was not

common in England before 1850. An approximately 35 % decrease in the severity of dental caries was experienced during World War II, but its prevalence increased after this temporary interruption (Sheiham 1984). The Vipeholm dental caries study in Sweden in the 1950s strongly linked the development and severity of dental caries in children to the frequent consumption of toffees (Krasse 2001). These compelling data derived from epidemiological studies support the theory that a cariogenic environment surrounding us contributes to the development of dental caries. However, it has long been known that there are noticeable individual variations in the susceptibility to dental caries (Mansbridge 1959).

The gene and environment interaction may better explain the true picture of dental caries pathophysiology. For many years, investigations in twins provided insight into the potential contribution of genetic factors. Monozygotic twins share the complete duplication of chromosomal DNA sequences that are not identical in dizygotic twins (Potter 1990). There are data indicating the significant similarities in the prevalence, location and severity of dental caries in monozygotic twins but not in dizygotic twins. Early studies demonstrated that monozygotic twins shared similarities in the number of teeth present, percentage of teeth and surfaces restored or carious, in addition to the tooth size and malocclusion (Boraas et al. 1988; Fairpo 1979). Similarly, a recent study on twins in Montes Claros, Brazil, supported these findings and further reported that the severity of dental caries at the same tooth surface was also similar between monozygotic twins (Bretz et al. 2005b).

One of the critiques of twin studies is that the reported similarity in the development of dental caries may be contributed not only by the shared genetic factor but also by the similar oral environment. In other words, these twins, particularly when they live in the same household, may be exposed to a similar cariogenic environment, which triggered the disease development. In fact, in the aforementioned Brazilian twin cohort, the measurements of lactic acid production by the biofilm on the tongue revealed that monozygotic twins showed significant similarities (Bretz et al.

2005a). Interestingly, it was further found that the lactic acid production of the oral biofilm was also identical in dizygotic twins. This finding supported the view that twins living in the same household exhibited a similar oral environment, possibly contributing to the development of dental caries. However, despite the similar oral environment, there were measurable discrepancies in dizygotic twins' dental caries experience, which thus could not be explained by their oral biofilm environment. Studies employing twins reared apart indicated the astonishing dental caries similarities in monozygotic twins after years of separate lives (Boraas et al. 1988; Conry et al. 1993). These data strongly support the theory that dental caries is developed not only by environmental causes but also by the genetic factors, which may determine the susceptibility of the patient. Today, it is postulated that genetic factors contribute up to 40 % to the development and severity of dental caries.

Although investigations are not extensive to date, twin studies indicated that the periodontal measurements such as probing depth, attachment loss and gingivitis (bleeding on probing) are more similar in monozygotic twins than dizygotic twins (Michalowicz et al. 2000; Rintakoski et al. 2010). These studies estimated the genetic contribution to periodontal disease to be 38–50 %.

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## 4.3 Gene and Environment of Implant Failure

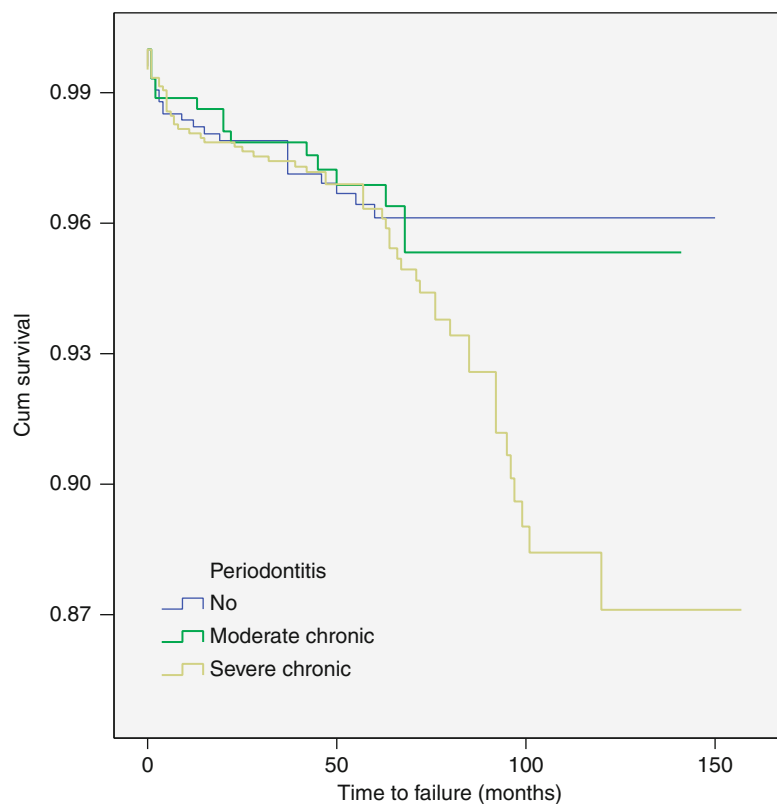
There is no twin study addressing the genetic involvement of implant failure in the literature to date. The clinical prerequisites involving twins having the same implant placement (Winkler et al. 2008) may make this type of investigation extremely challenging if not possible.

### 4.3.1 History of Chronic Periodontitis

Karoussis et al. (2003) reported a 10-year prospective cohort study of hollow screw ITI implants placed at the University of Berne School of Dental Medicine that the 10-year implant survival in



**Fig. 4.1** Long-term implant survival decreased in patients with a history of severe periodontitis (From Levin et al. 2011)



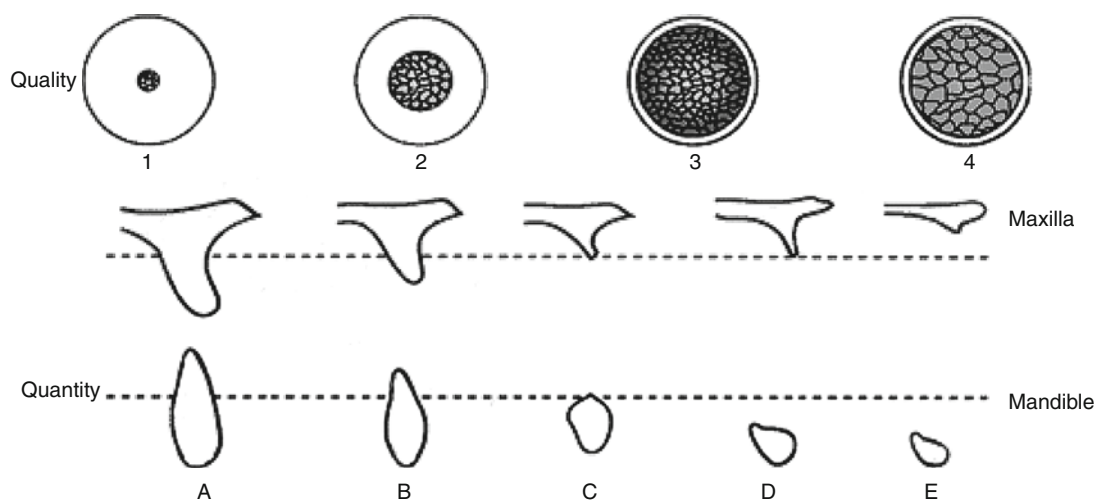
patients with the history of chronic periodontitis was 90.5 %, whereas 96.5 % of implants survived in patients without the periodontitis history. This study also suggested while the implant survival rates for the initial 5 years were above 98 % in both groups, the implants placed in patients with a history of chronic periodontitis constantly suffered from biological complications such as peri-implantitis (Karoussis et al. 2003). More recently, Levin et al. (2011) reported a historical prospective cohort study on the long-term implant survival recorded by a private practitioner at Kfar-Saba, Israel (Fig. 4.1). From the records of 717 patients with a total of 2,259 implants, a striking increase in late-stage failure was indicated in the group of patients with a history of severe chronic periodontitis. After 10 years, the implant survival plunged to 87 % in this group (Levin et al. 2011).

Reviews of these clinical studies highlight that patients with no history of periodontitis demonstrated a better outcome of long-term stability in implant treatment and that the failure rate in

patients with the history of periodontitis tended to be more prominent at the prosthetic phase (Klokkevold and Han 2007; Ong et al. 2008). These studies did not provide the possible cause of implant failure and the qualitative nature of peri-implant tissue evaluations were often less informative. However, it may be postulated that a combination of genetic and environmental factors that had initially caused severe periodontitis could later contribute to the implant failure.

#### 4.3.2 Quantity and Quality of Alveolar Bone

The extensive review of published data by Esposito et al. (1998) suggested a distinct trend of higher failure prevalence in implants placed in the maxillary molar region (Esposito et al. 1998). This may not be simply due to the factors associated with a maxillary location (Eckert and Wollan 1998) but rather due to the quantity and/or



**Fig. 4.2** Bone quality classification (Leckholm and Zarb) and bone quantity classification (Atwood)

quality of bone tissue at the maxillary molar site of implant placement, which may be attributed to one of the etiologic factors for dental implant failure (Jaffin and Berman 1991). Leckholm and Zarb (1985) proposed an index describing the operators' subjective assessment of alveolar bone quantity and quality (Lekholm and Zarb 1985) (Fig. 4.2).

Clinically, the maxillary posterior residual ridge was often classified as type 4 bone, depicting the thin cortical bone thickness with a less developed trabecular pattern. Therefore, it has been postulated that poor quality of alveolar residual ridge is a risk factor. In a retrospective cohort study of 4,680 implants over a 21-year period, Moy et al. (2005) reported the poor bone quality to be one of the associated factors for the increased implant failure (Moy et al. 2005).

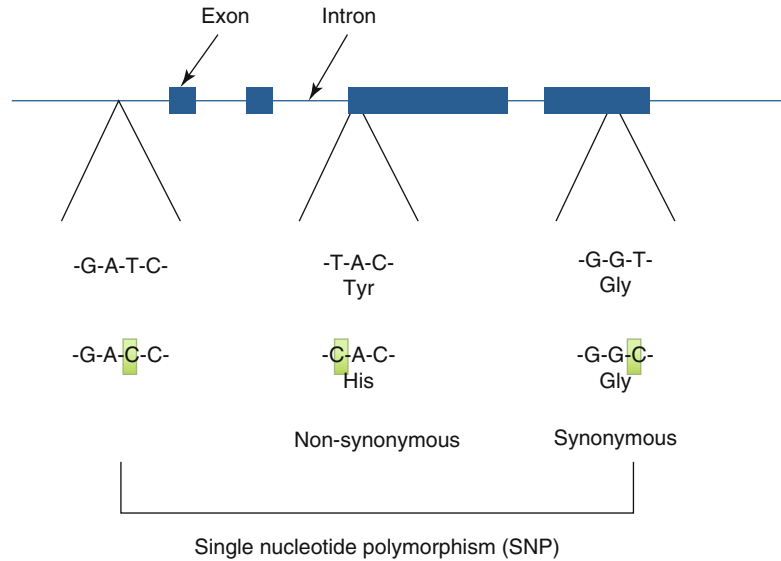
In a retrospective study, Hardt et al. (2002) reported that patients with a history of periodontitis appeared to develop poorer bone quantity (index D) but not bone quality (Hardt et al. 2002). The biological parameters contributing to the poor bone quantity and quality of alveolar residual ridge are still debated (Jahangiri et al. 1998; Kingsmill 1999). Nonetheless, it is highly conceivable that the genetic and environmental factors that contributed to the loss of

quantity and quality of alveolar bone may also affect the long-term stability of implant osseointegration.

#### 4.4 Implant Failure and Periodontitis-Associated Genes

With the advent of the human genome project and the successful completion of the entire genetic sequence of individuals with different ethnic backgrounds, the sequence mismatch between those individuals has generated a new concept of genetic contributions to common disease. Genetic diseases caused by genetic mutations such as craniosynostosis syndromes occur in less than 1 % of a given population by definition. On the contrary, genetic variations resulting from the gene sequence mismatch between individuals can occur more frequently, and thus, single gene sequence mismatch should not cause serious problems in an ordinary environment. However, when seemingly unrelated genetic variations are combined, the individual may develop a so-called common disease. It is also postulated that the combination of genetic variations and environmental conditions may collectively manifest the increased susceptibility.

**Fig. 4.3** Single-nucleotide polymorphism (SNP) presents the most frequent genomic variations. Some SNPs were found to modify the encoding amino acids. For example, TAC encodes for tyrosine. When T is substituted by C, CAC now encodes histidine. This type of SNP is called a non-synonymous SNP. Other SNPs such as GGT vs. GGC do not change the encoding amino acid (glycine), which is called a synonymous SNP



Variations in the DNA sequences are small in humans; however, they have been shown to cause diseases; to respond differently to pathogens, drugs or vaccines; and to determine the success and failure of certain treatments. A single-nucleotide polymorphism (SNP) presents the most frequent sequence variation (Fig. 4.3). SNP occurs approximately 1 in every 300 base pairs (bp) of human genome, which contains three billion bp. Along with the completion of more genetic sequences, increasing numbers of SNPs are updated in the publically available databases.

Many SNPs are found in protein non-coding domains or between active genes. Therefore, it is highly conceivable that these SNPs do not cause any serious problems. However, SNPs that are found in the protein-coding region may present profound manifestations. An amino acid unit of a protein is encoded by three base pairs (bp) of DNA, and an SNP within this region may result in an amino acid substitution (non-synonymous SNP). As a result, the variant of protein sequence may lead to an altered structural and functional property potentially causing a significant effect. Among all SNPs, however, non-synonymous SNPs form a small fraction.

Synonymous SNPs are also found to occur within the protein-coding domain called the exon in chromosomal DNA. This type of SNP does not

contribute to any modification in the protein sequence and thus is considered a “silent” SNP. The majority of SNPs are found in the non-coding domains such as introns, promoter regions and 3' regions. The putative effect of these SNPs has not been fully elucidated. It is possible that the function of chromosomal DNA, such as the rate of gene transcription, may be affected by SNPs located in the promoter region.

When the genetic material is inherited by offspring, parental DNAs are not admixed randomly but rather transferred as large sections. There is a strong tendency that even after many generations, these large sections are maintained in the chromosomal DNA of the offspring. The surviving large sections, called the “haplotype,” may contain the protein-coding sequences and their adjacent DNA sequences. Therefore, SNPs within the haplotype should show significant homology between the family members and to a large extent within the same ethnic groups. These SNP haplotypes provide useful information for elucidating the inheritance of a certain trait.

A simple oral rinse gives rise to an ample amount of chromosomal DNA from the patient, which may be applied for polymerase chain reaction (PCR) analysis of target SNPs. Statistical association between SNPs in the target genes and patients' phenotype (implant failure) has

established a new platform of investigation in dentistry (Nishimura and Garrett 2004).

#### 4.4.1 Interleukin-1 (IL-1)-Related Genes

Overzealous immunological reactions are believed to cause abnormal tissue destruction leading to periodontitis. Inflammatory cytokines are involved in the initiation and continuation of such immune reactions. Interleukin-1 (IL-1) has been long recognized in periodontal tissues and its relevance to the development of periodontitis has been established (Page 1991). IL-1 receptor recognizes both IL-1  $\alpha$  and IL-1 $\beta$ , which are encoded by distinct genes but share approximately 50 % sequence homology. IL-1 receptor also binds to IL-1 receptor antagonists (IL-1RA, encoded by IL-1RN gene). Whereas IL-1 $\alpha$  or IL-2 $\beta$  exerts downstream reactions after binding to IL-1 receptor, IL-1RA simply occupies the IL-1 receptor without any intracellular effects and thus is considered an inhibitor of IL-1 functions (Arend and Guthridge 2000). Among these IL-1-related molecules, it has been reported there is an increased level of IL-1 $\beta$  in gingival crevicular fluid associated with severe periodontitis (Chaudhari et al. 2011; Honig et al. 1989; Liu et al. 1996) and peri-implantitis (Curtis et al. 1997; Kao et al. 1995; Panagakos et al. 1996; Tsai et al. 1995).

Kornman et al. (1997) reported that the genotype exhibiting concurrent minor allele SNPs in IL-1 $\alpha$  (–889) and IL-1 $\beta$  (3953) were found to be more prevalent in non-smoker patients with severe chronic periodontitis (Kornman et al. 1997). Initially, the assay for IL-1 $\alpha$  (–889) SNP presented some technical difficulties. However, IL-1 $\alpha$  (–889) SNP was later found within the same “haplotype” of IL-1 $\alpha$  (4845) SNP. When we inherit the genetic information from our ancestors, a block of chromosome often containing multiple genes (called alleles) is transmitted as one piece. This piece of chromosomal fragment is called haplotype. In other words, the IL-1 $\alpha$  (–889) SNP located before the beginning of the IL-1 $\alpha$  coding sequence and IL-1 $\alpha$  (4845)

SNP located the end of IL-1 $\alpha$  coding sequence should be transmitted together over many generations. Therefore, the presence of IL-1 $\alpha$  (–889) SNP should be predicted by the test for IL-1 $\alpha$  (4845) SNP, which provided a technically feasible assay. Currently, SNPs of IL-1 $\alpha$  (–889) and IL-1 $\alpha$  (4845) are interchangeably used. It was also found that due to early sequence irregularities, IL-1 $\beta$  (3953) SNP may be interchangeably described as IL-1 $\beta$  (3954).

A commercially available clinical test of IL-1 SNPs was developed to determine the SNP minor alleles of IL-1 $\alpha$  (–889/4845) and IL-1 $\beta$  (3953/3954). PTS® genetic susceptibility test is the only commercially available SNP test in dentistry and currently distributed by Interleukin Genetics, Inc. and by OralDNA Labs (limited to the US market). In this test, patients who carry the minor allele of both IL-1 SNP sites would be informed of a potentially increased susceptibility to severe chronic periodontitis. The availability of the PTS® test may have contributed to the robust increase in genetic association studies for both periodontitis and implant failure (Table 4.1).

Feloutzis et al. (2003) investigated 180 patients, who received at least one ITI implant at the University of Berne (Feloutzis et al. 2003). In this study, 7 out of a total of 182 implants were lost during the loading period, all of which were placed in the maxilla of heavy smokers defined as 20 cigarettes per day for at least 20 years. For the remaining implants, the periapical radiographs taken during the multiple recall visits were used to measure the average loss of bone heights mesial and distal to the implant surface (the absolute bone loss, ABL). ABL as well as the bone loss per year was found to be significantly greater in the heavy smoker group; however, these peri-implant bone loss values were not associated with an IL-1 genotype based on the PTS® test (Feloutzis et al. 2003). Contrary to the hypothesis, there was a general but insignificant trend that IL-1 genotype positive patients showed smaller bone loss values as well as less bleeding-on-probing sites. When the smoking habits and IL-1 genotypes were combined, non-smokers or former smokers carrying the positive IL-1 genotypes indicated significantly

**Table 4.1** SNP genotypes of inflammation-related genes and implant failure

| Gene | SNP  | Association  | Implant failure phenotypes              | Smoking variant | Implant system   | Reference                      |
|------|------|--------------|-----------------------------------------|-----------------|------------------|--------------------------------|
| IL1A | -889 | None         | Mobility, pain in pre-prosthetic stages | Non-smokers     | 3I               | Campos et al. (2005a)          |
|      | -889 | None         | Biological complications                | Mixed           | Branemark System | Jansson et al. (2005)          |
|      | -889 | None         | Implant failure                         |                 |                  | Rogers et al. (2002)           |
|      | -889 | None         | Implant loss/biological complications   | Mixed           |                  | Vaz et al. (2011)              |
|      | -889 | None         | Lack of osseointegration                | Mixed           | ITI              | De Boever and De Boever (2006) |
|      | -889 | None         | Marginal bone loss at stage II surgery  |                 | Astra Tech       | Shimpuku et al. (2003)         |
|      | -889 | None         | Marginal bone loss >3 threads           | Mixed           | Branemark System | Laine et al. (2006)            |
|      | -889 | None         | Marginal bone loss at stage II surgery  | Mixed           |                  | Lin et al. (2007)              |
|      | 4845 | $p < 0.04$   | Marginal bone loss/year (protective?)   | Heavy smokers   | ITI              | Feloutzis et al. (2003)        |
|      | 4845 | $p = 0.0022$ | Biological complications                | Smokers         | ITI              | Gruica et al. (2004)           |
| IL1B | -511 | $p = 0.083$  | Loss of multiple implants               | Mixed           | NEODENT          | Dirschabel et al. (2011)       |
|      | -511 | $p = 0.033$  | Marginal bone loss at stage II surgery  |                 | Astra Tech       | Shimpuku et al. (2003)         |
|      | -551 | $p = 0.021$  | Marginal bone loss at stage II surgery  | Mixed           |                  | Lin et al. (2007)              |
|      | -511 | None         | Mobility, pain in pre-prosthetic stages | Non-smokers     | 3I               | Campos et al. (2005b)          |
|      | -511 | None         | Peri-implantitis                        |                 |                  | Melo et al. (2011)             |
|      | -511 | None         | Marginal bone loss >3 threads           | Mixed           | Branemark System | Laine et al. (2006)            |
|      | 3953 | None         | Mobility, pain in pre-prosthetic stages | Non-smokers     | 3I               | Campos et al. (2005a)          |
|      | 3953 | None         | Biological complications                | Mixed           | Branemark System | Jansson et al. (2005)          |
|      | 3953 | None         | Implant failure                         |                 |                  | Rogers et al. (2002)           |
|      | 3953 | None         | Implant loss/biological complications   | Mixed           |                  | Vaz et al. (2011)              |
|      | 3953 | None         | Lack of osseointegration                | Mixed           | ITI              | De Boever and De Boever (2006) |
|      | 3954 | $p < 0.04$   | Marginal bone loss/year (protective?)   | Heavy smokers   | ITI              | Feloutzis et al. (2003)        |
|      | 3954 | $p = 0.0022$ | Biological complications                | Smokers         | ITI              | Gruica et al. (2004)           |
|      | 3954 | None         | Biological complication                 | Mixed           | NEODENT          | Montes et al. (2009)           |
|      | 3954 | None         | Peri-implantitis                        |                 |                  | Melo et al. (2011)             |
|      | 3954 | None         | Marginal bone loss at stage II surgery  |                 | Astra Tech       | Shimpuku et al. (2003)         |
|      | 3954 | None         | Marginal bone loss >3 threads           | Mixed           | Branemark System | Laine et al. (2006)            |
|      | 3954 | None         | Marginal bone loss at stage II surgery  | Mixed           |                  | Lin et al. (2007)              |

| IL-RN        | Intron 2 | $p=0.029$ | Loss of multiple implants               | Mixed       | NEODENT          | Montes et al. (2009)     |
|--------------|----------|-----------|-----------------------------------------|-------------|------------------|--------------------------|
|              | Intron 2 | $p=0.02$  | Marginal bone loss >3 threads           |             | Branemark System | Laine et al. (2006)      |
|              | Intron 2 | None      | Mobility, pain in pre-prosthetic stages | Non-smokers | 3I               | Campos et al. (2005b)    |
| IL2          | -330     | None      | Mobility, pain in pre-prosthetic stages |             | Branemark System | Campos et al. (2005a)    |
| IL6          | -174     | None      | Peri-implantitis                        |             |                  | Melo et al. (2011)       |
|              | -174     | None      | Mobility, pain in pre-prosthetic stages |             | Branemark System | Campos et al. (2005a)    |
| IL10         | Promoter | None      | Implant loss                            |             | NEODENT          | Pigossi et al. (2012)    |
| TNF $\alpha$ | -308     | None      | Mobility, pain in pre-prosthetic stages |             | 3I               | Campos et al. (2004)     |
|              | -308     | None      | Peri-implantitis                        | Non-smokers |                  | Cury et al. (2009)       |
| TGF $\beta$  | -509     | None      | Mobility, pain in pre-prosthetic stages |             | 3I               | Dos Santos et al. (2004) |
|              | -800     | None      | Mobility, pain in pre-prosthetic stages |             | 3I               | Dos Santos et al. (2004) |
| MMP1         | -1607    | $p<0.001$ | Mobility, pain in pre-prosthetic stages |             | 3I               | Santos et al. (2004)     |
|              | -1607    | $p=0.046$ | Loss of implant during healing stage    | Non-smokers |                  | Arisan et al. (2005)     |
|              | -1607    | $p=0.011$ | Mobility, pain in pre-prosthetic stages |             |                  | Leite et al. (2008)      |
|              | -516     | None      | Mobility, pain in pre-prosthetic stages |             |                  | Leite et al. (2008)      |
| MMP9         | -1562    | None      | Mobility, pain in pre-prosthetic stages |             | 3I               | Santos et al. (2004)     |



less peri-implant bone loss (ABL and the bone loss per year). The smokers with the positive and negative IL-1 genotypes showed similar bone loss values. Therefore, if patients do not smoke, the data from this study suggest that the positive IL-1 genotype by PTS® test may indicate protection from the peri-implant bone loss.

Gruica et al. (2004) reported a follow-up study using the increased number of patients in the same institution (Gruica et al. 2004). This study included 180 patients and peri-implant biological complications were found associated with the longer number of years smoked ( $p=0.0101$ ) and the greater number of implants placed ( $p=0.0075$ ). On the contrary, IL-1 minor allele genotypes examined by PTS® test failed to show any correlation with peri-implant biological complications. However, detailed examinations revealed that 12 patients in this study were current heavy smokers carrying the IL-1 minor allele genotypes and 6 patients in this group exhibited biological complications. Periapical radiographs taken at recall visits of 1 and 8 years and radiographic peri-implant bone loss values were determined during this period of 7 years. The statistical evaluation using a generalized estimating equation suggested a correlation between IL-1 minor allele genotypes and peri-implant bone loss.

The IL-1 genotypes have been repeatedly examined in patients who have experienced implant failure or peri-implantitis. However, the results from all authors failed to establish the statistically significant correlation between IL-1 $\alpha$  (−889/4845) and IL-1 $\beta$  (3953/3954) dominant minor SNP alleles, with various biological complications associated with dental implants (Table 4.1) (Campos et al. 2005b; Jansson et al. 2005; Laine et al. 2006; Lin et al. 2007; Montes et al. 2009; Rogers et al. 2002; Shimpuku et al. 2003; Wilson and Nunn 1999). As such, the IL-1 $\alpha$  (−889/4845) and IL-1 $\beta$  (3953/3954) SNP genotype alone may not explain the cause of implants failure (Bormann et al. 2010).

Several investigations examined different SNP genotypes associated with IL-1 genes such as IL-1 $\beta$  (−511) or IL-1RN (intron 2) and found suggestive or strong correlations with the loss of multiple implants or marginal bone loss (Dirschmabel et al. 2011; Laine et al. 2006;

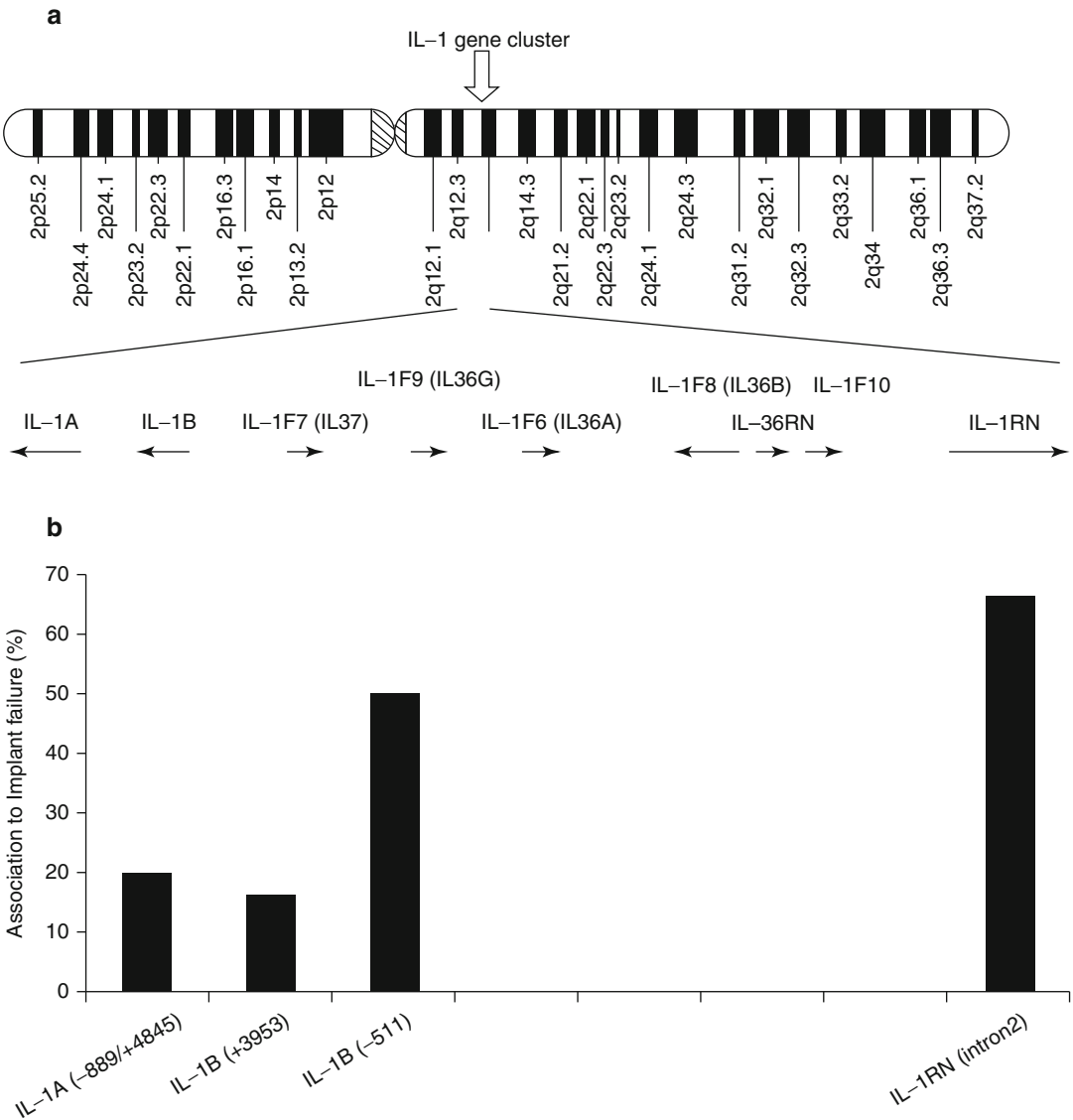
Lin et al. 2007; Montes et al. 2009; Shimpuku et al. 2003).

In a recent study, while statistical significance was not achieved, there was an increased trend of the prevalence of these SNP minor allele genotypes in patients experiencing peri-implantitis among the other evaluated implant-related biological complications (Vaz et al. 2011). Rogers et al. (2002) reported no significant correlation between the IL-1 $\alpha$  (−889/4845) and IL-1 $\beta$  (3953/3954) SNP genotype and implant failure; however, severe adult chronic periodontitis was significantly associated with IL-1 $\beta$  (3953/3954) SNP, but not IL-1 $\alpha$  (−889/4845) (Rogers et al. 2002).

The IL-1-related genes are located in close proximity within the approximately 300 Kb region chromosome 2q14 (Fig. 4.4a). The number of publications on the positive association of IL-1 genes with implant failure appeared to increase in the area between IL-1 $\beta$  (−511) and IL-1RN (intron 2) (Fig. 4.4b). Incidentally, an analysis of this IL-1 cluster region comparing 40 generalized aggressive periodontitis patients and 96 periodontally healthy subjects similarly reported the elevated association between IL-1 $\beta$  (−511) and IL-1RN (intron 2) (Fig. 4.4c) (Scapoli et al. 2005).

Melo et al. (2011) did not find any differences in the genotypic variations in IL-1 $\beta$  (3953/3954), IL-1 $\beta$  (−511) and IL-6 (−174) SNPs in peri-implantitis patients, and the same patient groups did not show the increase or decrease in the concentrations of IL-1b and IL-6 in the crevicular fluid sample obtained from healthy osseointegrated implants, peri-implantitis sites as well as healthy teeth (Melo et al. 2011). However, this study did not evaluate IL-1RN and IL-36RN.

IL-1RN and IL-36RN exhibit the opposite function to IL-1 $\beta$ . IL-1 $\beta$  is a potent pro-inflammatory cytokines, whose activities may be effectively inhibited by IL-1RN as well as IL-36RN. Furthermore, IL-1 $\beta$  is synthesized by macrophages and lymphocytes, whereas epithelial cells of the tongue and adipocytes and lymphocytes synthesize IL-1RN. Future studies may address the functional as well as genetic implications of IL-1 antagonist molecules in implant failure.



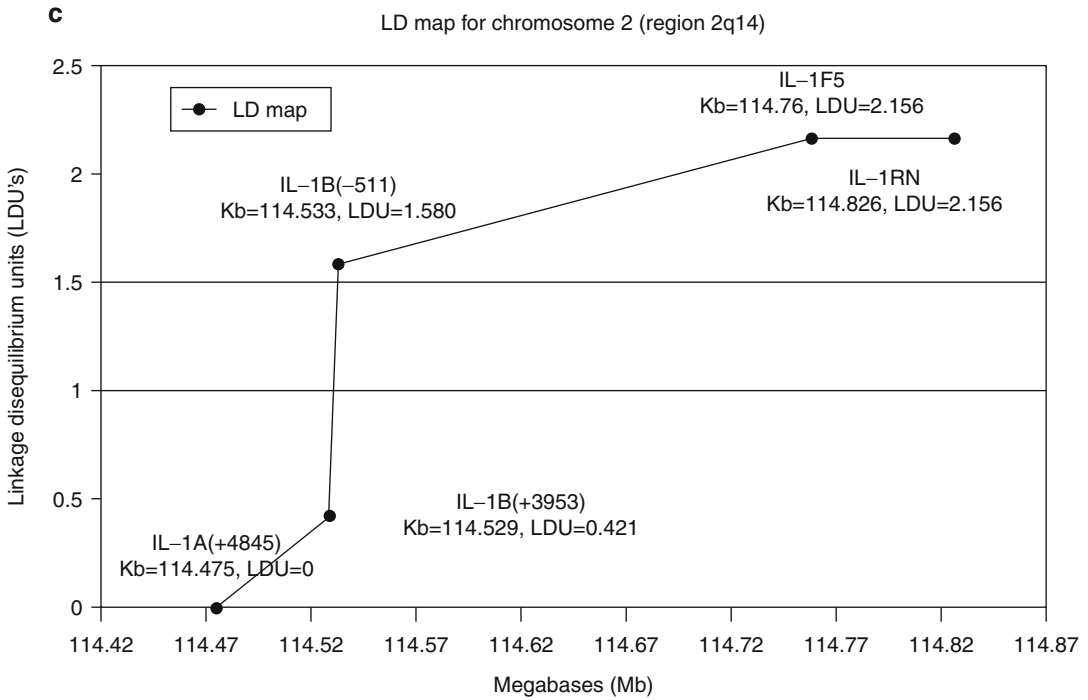
**Fig. 4.4** (a) Diagram of human chromosome 2. The IL-1-related genes are located in close proximity within the approximately 300 Kb region chromosome 2q14. (b). The number of published reports on the positive associa-

tion between implant failure and IL-1 cluster gene SNPs. (c) Linkage disequilibrium map of IL-1 cluster region for aggressive periodontitis (From Scapoli et al. 2005)

#### 4.4.2 Other Inflammatory Cytokines and Growth Factors

The complex network of inflammatory cytokines and their regulators are thought to play a central role in the pathological process of periodontitis. Antigen-activated T cells secrete IL-2, which further stimulates the growth of antigen-selected cytotoxic T cells. IL-1 $\beta$  and TNF $\alpha$  are also

pro-inflammatory cytokines associated with periodontitis. IL-6 works with osteoblasts and increases the secretion of receptor activator of nuclear factor kappa-B ligand (RANKL). Because RANKL is an essential signal for the differentiation of osteoclasts, IL-6 indirectly induces bone resorption. IL-10, an anti-inflammatory cytokine, can inhibit the synthesis of pro-inflammatory cytokines including IL-2 and TNF $\alpha$ . TGF $\beta$  may act as a growth



**Fig. 4.4** (continued)

factor and help in differentiating osteoblasts and wound-related fibroblast. Both IL-10 and TGF $\beta$  are decreased in experimentally induced periodontitis.

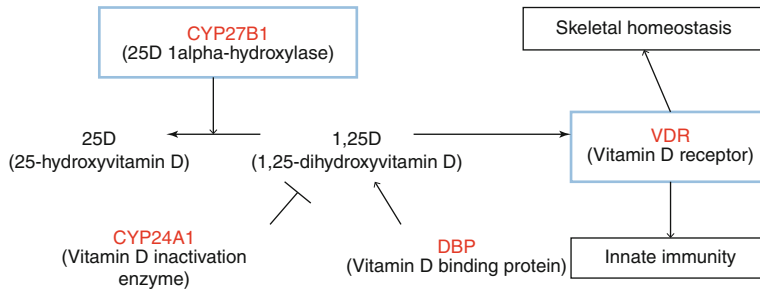
A number of investigations addressed potential associations with variations of these genes and aggressive forms of chronic periodontitis or early onset periodontitis (Laine et al. 2012; Zhang et al. 2011). Similarly, the genetic susceptibility of implant failure or biological complications has been investigated with these inflammatory cytokines and associated genes. However, these studies failed to identify the significant link to implant failure (Campos et al. 2004, 2005a; Cury et al. 2009; Dos Santos et al. 2004; Pigossi et al. 2012).

#### 4.4.3 Matrix Metalloproteinase 1 (MMP1)

Both periodontitis and implant biological complications involve periodontal tissue degradation including bone resorption and the loss of normal gingival connective tissue architecture.

Inflammatory cytokines stimulate the synthesis of matrix metalloproteinase 1 (MMP1), which is capable of degrading extracellular matrix such as collagens. Osteoclasts express MMP9, which plays a specific role in the bone environment.

Whereas the negative involvement of MMP9 genotype was reported (Santos et al. 2004), MMP1 (-1607) SNP was shown positively correlated to implant failure or biological complications (Arisan et al. 2005; Leite et al. 2008; Santos et al. 2004). MMP-1 (-1607) SNP has been found to increase the susceptibility of various diseases such as head and neck cancer metastasis or malignancy (Chaudhary, et al. 2010; Liu et al. 2012) and severe chronic periodontitis (de Souza et al. 2003; Loo et al. 2011). MMP-1 (-1607) SNP is composed of 1 G (glycine) or additional G insertion (2 G) genotypes and considered a functional polymorphism that patients with a 2 G genotype may increase the section of MMP-1 with or without periodontal inflammation (Repeke et al. 2009). Therefore, MMP-1 (-1607) 2 G genotype may increase the susceptibility to connective tissue degeneration particularly under unfavorable environmental conditions.



**Fig. 4.5** Genes involved in vitamin D system (red). Vitamin D metabolite, 25(OH)<sub>2</sub>D (25D) is a fat-soluble prohormone and is required to be activated by 25D 1alpha-hydroxylase (CYP27B1). The active form, 1,25(OH)<sub>2</sub>D

(1,25D), can be protected by the association with vitamin D-binding protein and can be degraded by the CYP24A1 enzyme. Vitamin D receptor (VDR) is a putative receptor of 1,25D and activates the gene transcription

## 4.5 Implant Failure and Genes Associated with Bone Quantity and/or Quality

### 4.5.1 X-Linked Hypophosphataemia and PHEX Gene Mutation

Rickets and osteomalacia are known to cause a significant reduction in bone quantity and quality. It was reported that there is a disproportionately high number of dental implant failures in X-linked hypophosphataemia (XLH) patients (Lekholm 2003). XLH is caused by a mutation in the phosphate-regulating endopeptidase gene (PHEX) located in chromosome Xp22.11. PHEX is a member of the cell surface metalloproteinases, primarily expressed by osteoblast-lineage cells (osteoblasts and osteocytes), and inactivating mutations may stimulate fibroblast growth factor 23 (FGF23) gene transcription. Processed FGF23 contributes to the phosphate re-adsorption in the renal tissue and critically maintains the phosphorus homeostasis. Unprocessed FGF23 due to the PHEX mutation inhibits the renal re-adsorption of phosphate resulting in hypophosphatemia.

The genetic mutation in XLH presents the loss of function of PHEX gene product, and clinical presentations vary from rickets with bone deformities to dental anomalies. Although the number of patients reporting implant failure is still small, the PHEX mutation associated with XLH may be considered a genetic contribution to implant failure. Further investigations on the genetic factors associated with these diseases may be warranted.

### 4.5.2 Vitamin D Axis Genes

XLH has been called “vitamin D-resistant rickets,” depicting the ineffectiveness of vitamin D supplement therapy using its precursor molecules. It is now understood that FGF23 suppresses the synthesis and stimulates the degradation of the active form of vitamin D, 1,25(OH)<sub>2</sub>D. Therefore, the overexpression of FGF23 may lead to vitamin D insufficiency without affecting the circulating vitamin D precursors. In fact, the majority of rickets and osteomalacia is caused by vitamin D insufficiency.

In order to address the potential role of vitamin D on implant osseointegration, the author’s group developed a nutritionally induced vitamin D-insufficient rat model and found that an experimental implant was poorly integrated under vitamin D insufficiency (Kelly et al. 2009; Mengatto et al. 2011). Implant failure in this animal model may point to the key role of vitamin D metabolism in osseointegration (Fig. 4.5).

After nutritional intake, vitamin D precursors such as cholecalciferol or ergocalciferol undergo several steps of molecular structural alterations. The exposure to ultraviolet light (UVB, 270–300 nm wavelength) is critical to synthesize the immediate precursor molecule, 25(OH)D, which circulates through the bloodstream. In various tissues, such as the kidney and bone, 25(OH)D is converted by the CYP27B1 enzyme to the active form of vitamin D, 1,25(OH)<sub>2</sub>D, which primarily acts as a hormone through the ligation to the putative vitamin D receptor (VDR). The VDR-1,25(OH)<sub>2</sub>D complex then functions with

the retinoic acid receptor (RXR) and regulates a wide range of gene transcription. The activity of  $1,25(\text{OH})_2\text{D}$  may be reduced by vitamin D-binding protein (DBP) and terminally deactivated by the CYP24A1 enzyme.

Therefore, the vitamin D axis genes should include VDR, CYP27B1, CYP24A1 and DBP. VDR SNP genotypes have been explored as restriction length polymorphisms such as BsmI (rs1544410), TaqI (rs731236), ApaI (rs7975232) and FokI (rs2228570). Among these, TaqI SNP of VDR has been linked to chronic severe periodontitis in the Italian (Martelli et al. 2011), Japanese (Tachi et al. 2003) and Chinese (Wang et al. 2009) populations. However, the investigation on TaqI SNP of VDR in osseointegration failure did not demonstrate a viable link (Alvim-Pereira et al. 2008). The possible involvement of other vitamin D axis genes has not been explored.

#### 4.5.3 FGFR1OP2/Wit3.0

Bone trabecular structure contributes to its mechanical strength. Imbalance between bone formation and resorption results in the long-term modification of trabecular structure, and the loss of bone trabeculae is believed to cause pathological bone fracture. Osteoporosis is an example of catabolic bone remodeling. Therefore, numerous studies have examined if patients with osteoporosis presented with an atrophic residual ridge. Radiographic bone trabecular structure of the mandible, for example, was intensely investigated for a correlation with the signs of osteoporosis. A recent review of the literature concluded that dental radiographs, particularly panoramic radiographs, can demonstrate an osteoporosis-associated bone loss at the mandibular ramus, inferior border and symphysis (Lopez-Lopez et al. 2011). The genetic factors contributing to the development of osteoporosis may also influence the alveolar bone quality.

The unique feature of residual ridge resorption is that the loss of height and width starts from the external surface of the alveolar bone and

appears to be independent from the internal trabecular architecture (Nishimura et al. 1992). After tooth extraction, the bony socket is eventually filled with newly formed trabecular bone by osteoblasts, whereas numerous osteoclasts are lined on the external alveolar bone surface facing the oral mucosa. Osteoclastogenesis involves an osteocyte-derived factor, receptor activator of nuclear factor kappa-B ligand (RANKL) (Nakashima et al. 2011; Xiong et al. 2011). What stimulates the osteocyte to synthesize RANKL is still largely unknown; however, the mechanosensor ability of osteocytes may trigger the osteoclastogenesis through RANKL production.

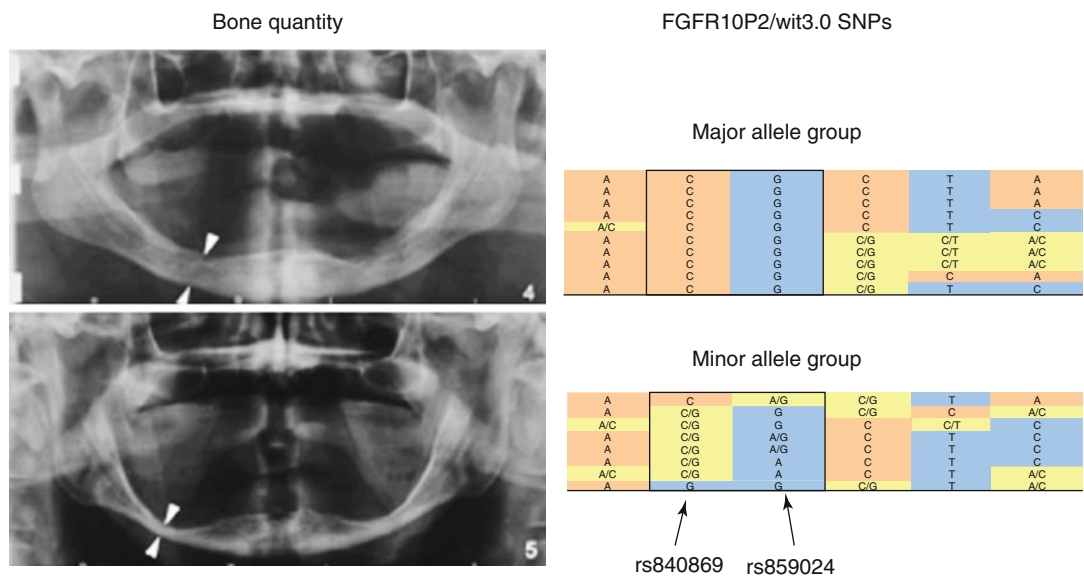
Osteocytes are embedded within the lacuna-canalicular network and are thought to detect mechanical strain. Excessive loading induces formation of microcracks in areas of cortical bone, which are eventually resorbed by osteoclasts. After the loss of the dentition, residual alveolar bone is covered by oral mucosa which undergoes significant wound healing. The author's group postulated that wound-associated oral mucosal contraction could induce an unusual mechanical tension to the underlying residual alveolar bone, which may be sensed by the osteocytes leading to continuous localized bone resorption. The recent discovery of a novel cytoskeleton molecule, wound-inducible transcript 3.0 (wit3.0), from gingival tissue at the tooth extraction site, suggested that the overexpression of wit3.0 resulted in increased wound contraction. Wit3.0 was encoded by the FGFR1OP2 gene. Totally edentulous patients carrying minor SNP alleles of FGFR1OP2/wit3.0 were found to exhibit severely atrophic mandibular residual ridge (Fig. 4.6). These studies suggest that FGFR1OP2/wit3.0 may contribute to an insufficient bone quantity for implant therapy.

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## 4.6 Conclusion and Future Perspectives

### 4.6.1 Unexplored Genetic Variations

The human genome project uncovered a previously unknown variation that the copy number of an allele may also be different among

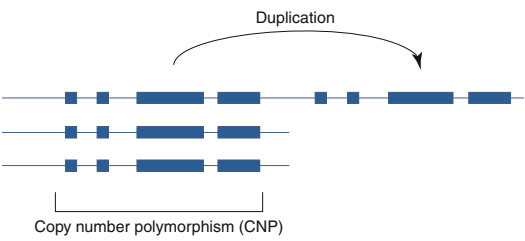


**Fig. 4.6** After tooth extraction, edentulous residual alveolar bone continues bone resorption. Two SNPs in FGFR10P2/wit3.0 have been associated with the bone quantity of mandibular edentulous jaws (From Suwanwela et al. (2011))

individuals. It was believed that the chromosome in a somatic cell is composed of a pair of maternal and paternal genes, in other words, two copies per gene. However, duplications and deletions of chromosome sections were found to be more prevalent, resulting in the variation in the copy number of genes or copy number polymorphisms (CNP) (Sebat et al. 2004). The effect of CNP is readily apparent that the abundance of encoded proteins must be linearly associated with the available gene copy number (Fig. 4.7). The investigation on CNP, however, requires extensive research tools and thus has not been fully engaged for dental diseases (Stokes et al. 2011).

**4.6.2 Summary and Conclusions**

The inquiry for possible genetic contributions to late-stage implant failure has been a “hot” area of investigation. Cohorts of patients presenting implant failure or biological complications provided important opportunities to study such genetic contributions. However, the approach has been limited to the periodontitis model addressing if genes with a reported correlation to periodontitis similarly associate with implant failure.



**Fig. 4.7** Copy number polymorphism (CNP) was found more prevalent than once believed. The increasing copy number may result in the increased protein expression

These studies certainly identified the IL-1 cluster and MMP-1 as possible genes linked to implant failure. An important question still remains: Is the bone resorption contributing to the late-stage implant failure caused by the same mechanism as periodontitis?

A recent understanding of the role of osteocytes for inducing osteoclasts may open a new avenue of investigation for elucidating implant-associated bone resorption. The close proximity of alveolar bone to oral mucosa, one of the most active barrier tissues, may also direct our studies in a new direction.

Traditionally, dental examination included only a few clinical tests, such as vitality testing of



teeth and dental radiography. While genetic association research uncovers important genotypes highly relevant to clinical dentistry, serious efforts may be required to facilitate an entirely new field of dental clinical examination. Because chromosomal DNA can be easily collected from either a buccal swab or oral rinse samples, dentists are well positioned to centrally participate in the field of genetic diagnosis in the future.

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## References

- Alvim-Pereira F, Montes CC, Thome G, Olandoski M, Trevilatto PC (2008) Analysis of association of clinical aspects and vitamin D receptor gene polymorphism with dental implant loss. *Clin Oral Implants Res* 19(8):786–795
- Arend WP, Guthridge CJ (2000) Biological role of interleukin 1 receptor antagonist isoforms. *Ann Rheum Dis* 59(Suppl 1):i60–i64
- Arisan V, Karabuda C, Özdemir T (2005) Effect of MMP-1 polymorphism on early term osseointegrated dental implant failure: a pilot study. *J Cell Mol Biol* 4:53–58
- Attard NJ, Zarb GA (2005) Immediate and early implant loading protocols: a literature review of clinical studies. *J Prosthet Dent* 94(3):242–258
- Balshe AA, Assad DA, Eckert SE, Koka S, Weaver AL (2009) A retrospective study of the survival of smooth- and rough-surface dental implants. *Int J Oral Maxillofac Implants* 24(6):1113–1118
- Boraas JC, Messer LB, Till MJ (1988) A genetic contribution to dental caries, occlusion, and morphology as demonstrated by twins reared apart. *J Dent Res* 67(9):1150–1155
- Bormann KH, Stuhmer C, Z'Graggen M, Kokemoller H, Rucker M, Gellrich NC (2010) IL-1 polymorphism and periimplantitis. A literature review. *Schweiz Monatsschr Zahnmed* 120(6):510–520
- Bowen WH, Koo H (2011) Biology of *Streptococcus mutans*-derived glucosyltransferases: role in extracellular matrix formation of cariogenic biofilms. *Caries Res* 45(1):69–86
- Bretz WA, Corby PM, Hart TC, Costa S, Coelho MQ, Weyant RJ et al (2005a) Dental caries and microbial acid production in twins. *Caries Res* 39(3):168–172
- Bretz WA, Corby PM, Schork NJ, Robinson MT, Coelho M, Costa S et al (2005b) Longitudinal analysis of heritability for dental caries traits. *J Dent Res* 84(11):1047–1051
- Campos MI, dos Santos MC, Trevilatto PC, Scarel-Caminaga RM, Bezerra FJ, Line SR (2004) Early failure of dental implants and TNF-alpha (G-308A) gene polymorphism. *Implant Dent* 13(1):95–101
- Campos MI, Godoy dos Santos MC, Trevilatto PC, Scarel-Caminaga RM, Bezerra FJ, Line SR (2005a) Interleukin-2 and interleukin-6 gene promoter polymorphisms, and early failure of dental implants. *Implant Dent* 14(4):391–396
- Campos MI, Santos MC, Trevilatto PC, Scarel-Caminaga RM, Bezerra FJ, Line SR (2005b) Evaluation of the relationship between interleukin-1 gene cluster polymorphisms and early implant failure in non-smoking patients. *Clin Oral Implants Res* 16(2):194–201
- Chaudhari AU, Byakod GN, Waghmare PF, Karhadkar VM (2011) Correlation of levels of interleukin-1beta in gingival crevicular fluid to the clinical parameters of chronic periodontitis. *J Contemp Dent Pract* 12(1):52–59
- Chaudhary AK, Pandya S, Mehrotra R, Bharti AC, Jain S, Singh M (2010) Functional polymorphism of the MMP-1 promoter (-1607 1 G/2G) in potentially malignant and malignant head and neck lesions in an Indian population. *Biomarkers* 15(8):684–692
- Chuang SK (2005) Jawbone quality, jaw shape, implant length, and overdenture treatment protocol were associated with implant failures. *J Evid Based Dent Pract* 5(4):215–216
- Chuang SK, Tian L, Wei LJ, Dodson TB (2002a) Predicting dental implant survival by use of the marginal approach of the semi-parametric survival methods for clustered observations. *J Dent Res* 81(12):851–855
- Chuang SK, Wei LJ, Douglass CW, Dodson TB (2002b) Risk factors for dental implant failure: a strategy for the analysis of clustered failure-time observations. *J Dent Res* 81(8):572–577
- Conry JP, Messer LB, Boraas JC, Aeppli DP, Bouchard TJ Jr (1993) Dental caries and treatment characteristics in human twins reared apart. *Arch Oral Biol* 38(11):937–943
- Cooper LF (2000) A role for surface topography in creating and maintaining bone at titanium endosseous implants. *J Prosthet Dent* 84(5):522–534
- Curtis DA, Kao R, Plesh O, Finzen F, Franz L (1997) Crevicular fluid analysis around two failing dental implants: a clinical report. *J Prosthodont* 6(3):210–214
- Cury PR, Horewicz VV, Ferrari DS, Brito R Jr, Sendyk WR, Duarte PM et al (2009) Evaluation of the effect of tumor necrosis factor-alpha gene polymorphism on the risk of peri-implantitis: a case-control study. *Int J Oral Maxillofac Implants* 24(6):1101–1105
- De Boever AL, De Boever JA (2006) Early colonization of non-submerged dental implants in patients with a history of advanced aggressive periodontitis. *Clin Oral Implants Res* 17(1):8–17

- de Souza AP, Trevilatto PC, Scarel-Caminaga RM, Brito RB, Line SR (2003) MMP-1 promoter polymorphism: association with chronic periodontitis severity in a Brazilian population. *J Clin Periodontol* 30(2): 154–158
- Dirschsnabel AJ, Alvim-Pereira F, Alvim-Pereira CC, Bernardino JF, Rosa EA, Trevilatto PC (2011) Analysis of the association of IL1B(C-511 T) polymorphism with dental implant loss and the clusterization phenomenon. *Clin Oral Implants Res* 22(11):1235–1241
- Dos Santos MC, Campos MI, Souza AP, Scarel-Caminaga RM, Mazzonetto R, Line SR (2004) Analysis of the transforming growth factor-beta 1 gene promoter polymorphisms in early osseointegrated implant failure. *Implant Dent* 13(3):262–269
- Eckert SE, Wollan PC (1998) Retrospective review of 1170 endosseous implants placed in partially edentulous jaws. *J Prosthet Dent* 79(4):415–421
- Esposito M, Hirsch JM, Lekholm U, Thomsen P (1998) Biological factors contributing to failures of osseointegrated oral implants (I) Success criteria and epidemiology. *Eur J Oral Sci* 106(1):527–551
- Fairpo CG (1979) Total caries experience in monozygotic and like-sexed dizygotic twins of caucasoid origin aged 5 to 15 years. *Arch Oral Biol* 24(7):491–494
- Feloutzis A, Lang NP, Tonetti MS, Burgin W, Bragger U, Buser D et al (2003) IL-1 gene polymorphism and smoking as risk factors for peri-implant bone loss in a well-maintained population. *Clin Oral Implants Res* 14(1):10–17
- Friberg B, Nilson H, Olsson M, Palmquist C (1997) Mk II: the self-tapping Branemark implant: 5-year results of a prospective 3-center study. *Clin Oral Implants Res* 8(4):279–285
- Gruica B, Wang HY, Lang NP, Buser D (2004) Impact of IL-1 genotype and smoking status on the prognosis of osseointegrated implants. *Clin Oral Implants Res* 15(4):393–400
- Hardt CR, Grondahl K, Lekholm U, Wennstrom JL (2002) Outcome of implant therapy in relation to experienced loss of periodontal bone support: a retrospective 5-year study. *Clin Oral Implants Res* 13(5):488–494
- Honig J, Rordorf-Adam C, Siegmund C, Wiedemann W, Erard F (1989) Increased interleukin-1 beta (IL-1 beta) concentration in gingival tissue from periodontitis patients. *J Periodontol Res* 24(6):362–367
- Jaffin RA, Berman CL (1991) The excessive loss of Branemark fixtures in type IV bone: a 5-year analysis. *J Periodontol* 62(1):2–4
- Jahangiri L, Devlin H, Ting K, Nishimura I (1998) Current perspectives in residual ridge remodeling and its clinical implications: a review. *J Prosthet Dent* 80(2):224–237
- Jansson H, Hamberg K, De Bruyn H, Bratthall G (2005) Clinical consequences of IL-1 genotype on early implant failures in patients under periodontal maintenance. *Clin Implant Dent Relat Res* 7(1):51–59
- Jemt T, Hager P (2006) Early complete failures of fixed implant-supported prostheses in the edentulous maxilla: a 3-year analysis of 17 consecutive cluster failure patients. *Clin Implant Dent Relat Res* 8(2):77–86
- Kao RT, Curtis DA, Richards DW, Preble J (1995) Increased interleukin-1 beta in the crevicular fluid of diseased implants. *Int J Oral Maxillofac Implants* 10(6):696–701
- Karoussis IK, Salvi GE, Heitz-Mayfield LJ, Bragger U, Hammerle CH, Lang NP (2003) Long-term implant prognosis in patients with and without a history of chronic periodontitis: a 10-year prospective cohort study of the ITI Dental Implant System. *Clin Oral Implants Res* 14(3):329–339
- Kelly J, Lin A, Wang CJ, Park S, Nishimura I (2009) Vitamin D and bone physiology: demonstration of vitamin D deficiency in an implant osseointegration rat model. *J Prosthodont* 18(6):473–478
- Kingsmill VJ (1999) Post-extraction remodeling of the adult mandible. *Crit Rev Oral Biol Med* 10(3): 384–404
- Kleinberg I (2002) A mixed-bacteria ecological approach to understanding the role of the oral bacteria in dental caries causation: an alternative to *Streptococcus mutans* and the specific-plaque hypothesis. *Crit Rev Oral Biol Med* 13(2):108–125
- Klokkevold PR, Han TJ (2007) How do smoking, diabetes, and periodontitis affect outcomes of implant treatment? *Int J Oral Maxillofac Implants* 22(Suppl):173–202
- Kornman KS, Crane A, Wang HY, di Giovine FS, Newman MG, Pirk FW et al (1997) The interleukin-1 genotype as a severity factor in adult periodontal disease. *J Clin Periodontol* 24(1):72–77
- Krasse B (2001) The Vipeholm Dental Caries Study: recollections and reflections 50 years later. *J Dent Res* 80(9):1785–1788
- Laine ML, Leonhardt A, Roos-Jansaker AM, Pena AS, van Winkelhoff AJ, Winkel EG et al (2006) IL-1RN gene polymorphism is associated with peri-implantitis. *Clin Oral Implants Res* 17(4):380–385
- Laine ML, Crielaard W, Loos BG (2012) Genetic susceptibility to periodontitis. *Periodontol* 2000 58(1):37–68
- Leite MF, Santos MC, de Souza AP, Line SR (2008) Osseointegrated implant failure associated with MMP-1 promoter polymorphisms (-1607 and -519). *Int J Oral Maxillofac Implants* 23(4):653–658
- Lekholm U (2003) Immediate/early loading of oral implants in compromised patients. *Periodontol* 2000 33(3):194–203
- Lekholm U, Zarb GA (1985) Patient selection and preparation. In: Branemark PI, Zarb GA, Albrektsson T (eds) *Tissue-integrated prostheses: osseointegration in clinical dentistry*. Quintessence Publishing Co, Chicago, pp 199–209
- Levin L, Ofec R, Grossmann Y, Anner R (2011) Periodontal disease as a risk for dental implant failure over time: a long-term historical cohort study. *J Clin Periodontol* 38(8):732–737
- Lin YH, Huang P, Lu X, Guan DH, Man Y, Wei N et al (2007) The relationship between IL-1 gene polymorphism and marginal bone loss around dental implants. *J Oral Maxillofac Surg* 65(11):2340–2344

- Liu CM, Hou LT, Wong MY, Rossomando EF (1996) Relationships between clinical parameters, Interleukin 1B and histopathologic findings of gingival tissue in periodontitis patients. *Cytokine* 8(2):161–167
- Liu D, Guo H, Li Y, Xu X, Yang K, Bai Y (2012) Association between polymorphisms in the promoter regions of matrix metalloproteinases (MMPs) and risk of cancer metastasis: a meta-analysis. *PLoS One* 7(2):e31251
- Loo WT, Wang M, Jin LJ, Cheung MN, Li GR (2011) Association of matrix metalloproteinase (MMP-1, MMP-3 and MMP-9) and cyclooxygenase-2 gene polymorphisms and their proteins with chronic periodontitis. *Arch Oral Biol* 56(10):1081–1090
- Lopez-Lopez J, Estrugo-Devesa A, Jane-Salas E, Ayuso-Montero R, Gomez-Vaquero C (2011) Early diagnosis of osteoporosis by means of orthopantomograms and oral x-rays: a systematic review. *Medicina Oral Patol Oral Cir Bucal* 16(7):e905–e913
- Mansbridge JN (1959) Heredity and dental caries. *J Dent Res* 38(2):337–347
- Marie PJ, Coffin JD, Hurley MM (2005) FGF and FGFR signaling in chondrodysplasias and craniosynostosis. *J Cell Biochem* 96(5):888–896
- Martelli FS, Mengoni A, Martelli M, Rosati C, Fanti E (2011) VDR TaqI polymorphism is associated with chronic periodontitis in Italian population. *Arch Oral Biol* 56(12):1494–1498
- Melo RF, Lopes BM, Shibli JA, Marcantonio Junior E, Marcantonio RA, Galli GM (2011). Interleukin-1 beta and Interleukin-6 expression and gene polymorphisms in subjects with peri-implant disease. *Clin Implant Dent Relat Res*. 2011 Mar 17. doi: [10.1111/j.1708-8208.2010.00325.x](https://doi.org/10.1111/j.1708-8208.2010.00325.x). [Epub ahead of print]
- Melville H, Wang Y, Taub PJ, Jabs EW (2010) Genetic basis of potential therapeutic strategies for craniosynostosis. *Am J Med Genet A* 152A(12):3007–3015
- Mendonca G, Mendonca DB, Aragao FJ, Cooper LF (2008) Advancing dental implant surface technology—from micron- to nanotopography. *Biomaterials* 29(28):3822–3835
- Mengatto CM, Mussano F, Honda Y, Colwell CS, Nishimura I (2011) Circadian rhythm and cartilage extracellular matrix genes in osseointegration: a genome-wide screening of implant failure by vitamin D deficiency. *PLoS One* 6(1):e15848
- Michalowicz BS, Diehl SR, Gunsolley JC, Sparks BS, Brooks CN, Koertge TE et al (2000) Evidence of a substantial genetic basis for risk of adult periodontitis. *J Periodontol* 71(11):1699–1707
- Montes CC, Alvim-Pereira F, de Castilhos BB, Sakurai ML, Olandoski M, Trevilatto PC (2009) Analysis of the association of IL1B (C+3954 T) and IL1RN (intron 2) polymorphisms with dental implant loss in a Brazilian population. *Clin Oral Implants Res* 20(2):208–217
- Moy PK, Medina D, Shetty V, Aghaloo TL (2005) Dental implant failure rates and associated risk factors. *Int J Oral Maxillofac Implants* 20(4):569–577
- Nakashima T, Hayashi M, Fukunaga T, Kurata K, Oh-Hora M, Feng JQ et al (2011) Evidence for osteocyte regulation of bone homeostasis through RANKL expression. *Nat Med* 17(10):1231–1234
- Nishimura I, Garrett N (2004) Impact of Human Genome Project on treatment of frail and edentulous patients. *Gerodontology* 21(1):3–9
- Nishimura I, Hosokawa R, Atwood DA (1992) The knife-edge tendency in mandibular residual ridges in women. *J Prosthet Dent* 67(6):820–826
- Ong CT, Ivanovski S, Needleman IG, Retzepi M, Moles DR, Tonetti MS et al (2008) Systematic review of implant outcomes in treated periodontitis subjects. *J Clin Periodontol* 35(5):438–462
- Paes Leme AF, Koo H, Bellato CM, Bedi G, Cury JA (2006) The role of sucrose in cariogenic dental biofilm formation—new insight. *J Dent Res* 85(10):878–887
- Page RC (1991) The role of inflammatory mediators in the pathogenesis of periodontal disease. *J Periodontol Res* 26(3 Pt 2):230–242
- Panagakos FS, Aboyoussef H, Dondero R, Jandinski JJ (1996) Detection and measurement of inflammatory cytokines in implant crevicular fluid: a pilot study. *Int J Oral Maxillofac Implants* 11(6):794–799
- Pigossi SC, Alvim-Pereira F, Montes CC, Finoti LS, Secolin R, Trevilatto PC et al (2012) Genetic association study between Interleukin 10 gene and dental implant loss. *Arch Oral Biol* 57(9):1256–1263
- Potter RH (1990) Twin half-sibs: a research design for genetic epidemiology of common dental disorders. *J Dent Res* 69(8):1527–1530
- Repeke CE, Trombone AP, Ferreira SB Jr, Cardoso CR, Silveira EM, Martins W Jr et al (2009) Strong and persistent microbial and inflammatory stimuli overcome the genetic predisposition to higher matrix metalloproteinase-1 (MMP-1) expression: a mechanistic explanation for the lack of association of MMP1-1607 single-nucleotide polymorphism genotypes with MMP-1 expression in chronic periodontitis lesions. *J Clin Periodontol* 36(9):726–738
- Rintakoski K, Kaprio J, Murtomaa H (2010) Genetic and environmental factors in oral health among twins. *J Dent Res* 89(7):700–704
- Rogers MA, Figliomeni L, Baluchova K, Tan AE, Davies G, Henry PJ et al (2002) Do interleukin-1 polymorphisms predict the development of periodontitis or the success of dental implants? *J Periodontol Res* 37(1):37–41
- Santos MC, Campos MI, Souza AP, Trevilatto PC, Line SR (2004) Analysis of MMP-1 and MMP-9 promoter polymorphisms in early osseointegrated implant failure. *Int J Oral Maxillofac Implants* 19(1):38–43
- Scapoli C, Trombelli L, Mamolini E, Collins A (2005) Linkage disequilibrium analysis of case-control data: an application to generalized aggressive periodontitis. *Genes Immun* 6(1):44–52
- Schwartz-Arad D, Laviv A, Levin L (2008) Failure causes, timing, and cluster behavior: an 8-year study of dental implants. *Implant Dent* 17(2):200–207

- Sebat J, Lakshmi B, Troge J, Alexander J, Young J, Lundin P et al (2004) Large-scale copy number polymorphism in the human genome. *Science* 305(5683):525–528
- Sheiham A (1984) Changing trends in dental caries. *Int J Epidemiol* 13(2):142–147
- Shimpuku H, Nosaka Y, Kawamura T, Tachi Y, Shinohara M, Ohura K (2003) Genetic polymorphisms of the interleukin-1 gene and early marginal bone loss around endosseous dental implants. *Clin Oral Implants Res* 14(4):423–429
- Smith EG, Spatafora GA (2012) Gene regulation in *S. mutans*: complex control in a complex environment. *J Dent Res* 91(2):133–141
- Stanford CM (2007) Dental implants. A role in geriatric dentistry for the general practice? *J Am Dent Assoc* 138(Suppl):34S–40S
- Stokes A, Drozdov I, Guerra E, Ouzounis CA, Warnakulasuriya S, Gleeson MJ et al (2011) Copy number and loss of heterozygosity detected by SNP array of formalin-fixed tissues using whole-genome amplification. *PLoS One* 6(9):e24503
- Suwanwela J, Lee J, Lin A, Ucer TC, Devlin H, Sinsheimer J, Garrett NR, Nishimura I (2011) A genetic association study of single-nucleotide polymorphisms in *FGFR1OP2/wit3.0* and long-term atrophy of edentulous mandible. *PLoS One* 19(6):e16204
- Tachi Y, Shimpuku H, Nosaka Y, Kawamura T, Shinohara M, Ueda M et al (2003) Vitamin D receptor gene polymorphism is associated with chronic periodontitis. *Life Sci* 73(26):3313–3321
- Tsai CC, Ho YP, Chen CC (1995) Levels of interleukin-1 beta and interleukin-8 in gingival crevicular fluids in adult periodontitis. *J Periodontol* 66(10):852–859
- Vaz P, Gallas MM, Braga AC, Sampaio-Fernandes JC, Felino A, Tavares P (2011) IL1 gene polymorphisms and unsuccessful dental implants. *Clin Oral Implants Res*. doi: [10.1111/j.1600-0501.2011.02322.x](https://doi.org/10.1111/j.1600-0501.2011.02322.x)
- Wang C, Zhao H, Xiao L, Xie C, Fan W, Sun S et al (2009) Association between vitamin D receptor gene polymorphisms and severe chronic periodontitis in a Chinese population. *J Periodontol* 80(4):603–608
- Wilson TG Jr, Nunn M (1999) The relationship between the interleukin-1 periodontal genotype and implant loss. Initial data. *J Periodontol* 70(7):724–729
- Winkler S, Boberick KG, Braid S, Wood R, Cari MJ (2008) Implant replacement of congenitally missing lateral incisors: a case report. *J Oral Implantol* 34(2):115–118
- Xiong J, Onal M, Jilka RL, Weinstein RS, Manolagas SC, O'Brien CA (2011) Matrix-embedded cells control osteoclast formation. *Nat Med* 17(10):1235–1241
- Zhang J, Sun X, Xiao L, Xie C, Xuan D, Luo G (2011) Gene polymorphisms and periodontitis. *Periodontol* 2000 56(1):102–124

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## 5.1 Introduction: Bisphosphonates

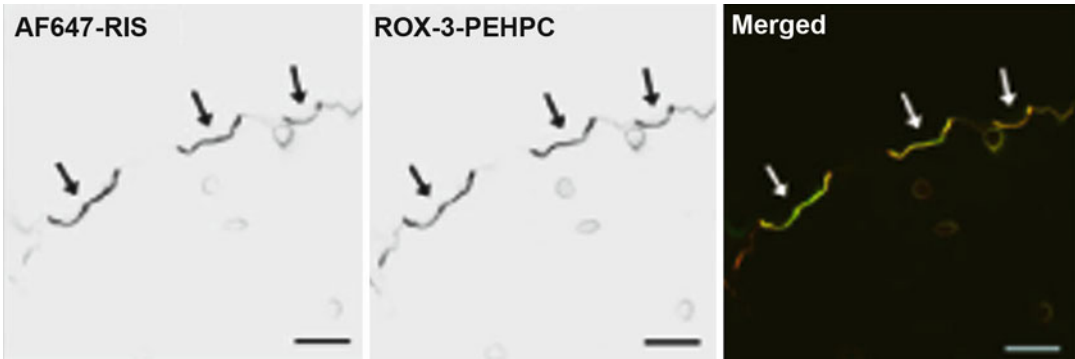
Bisphosphonates (BP) are synthetic pyrophosphates possessing a strong affinity to calcium and magnesium ions as well as biologically generated hydroxyapatite. The first successful chemical synthesis of 1-hydroxy-1,1-ethylidene bisphosphonate disodium salt (etidronate) was reported by Von Baeyer and Hoffmann in 1897 (Francis and Valent 2007). However, BPs had no known uses until the first experimental application in dentistry. Then, in the 1960s, calcium-chelating agents were actively examined for possible efficacy in removing dental calculus; however, many of these agents not only removed calculus but also etched enamel and caused damage. When etidronate was tested, the highly polished enamel surface was not damaged (Briner and Francis 1973). This observation has inspired further studies about the adsorption of BPs onto hydroxyapatite surfaces.

Unlike other pyrophosphate molecules, BPs exhibit a distinct chemical stability. Once adsorbed onto hydroxyapatite, BPs form a thin layer on the external surface of bone, enamel, and dentin, preventing further apposition of calcium phosphate (Fig. 5.1). Thus, until osteoclasts remove the BP-containing mineral from bone, BPs are believed to stay on the bone surface for an extended period.

The common structure of BPs contains two phosphates atoms connected by a hydroxycarbon backbone, which can form a structure responsible

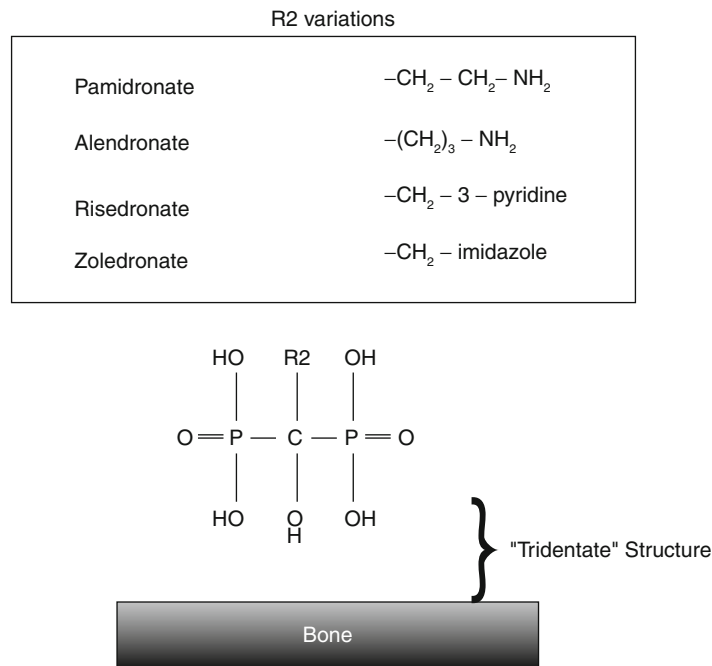
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**Fig. 5.1** Fluorescent-labeled risedronates were injected into 9-week-old rats and 24 h later, the tibia was harvested. Thin layers of the fluorescent activity were observed at the bone resorption lacunae (*arrows*) (From Roelofs et al. (2012))

**Fig. 5.2** The common structure of nitrogen-containing BPs. The strong affinity to hydroxyapatite is accommodated by two phosphates and hydroxyl R1 chain. The R2 chain varies among different BPs; however, the current generation of BPs contains a nitrogen molecule



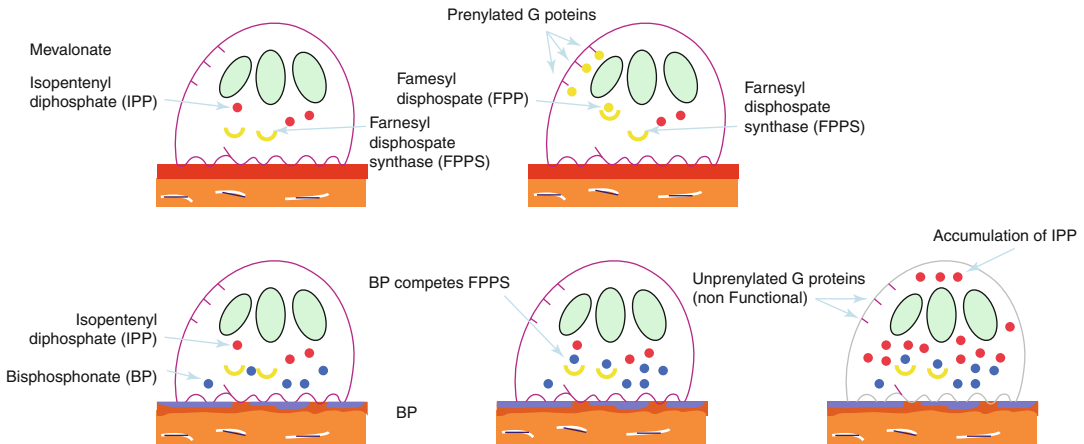
for the strong affinity to calcium ions. One remaining side chain (R2 chain) represents the molecular and functional variations of BPs. The current generation of BPs contains a nitrogen atom in the R2 chain and thus is called a nitrogen-containing BP or aminobisphosphonate (Fig. 5.2).

The first experimental use of BP in humans was to treat a fibrodysplasia ossificans progressiva (FOP) patient. FOP patients carry rare genetic mutations in activin-like kinase-2

associated with BMP type 1 receptor, which causes heterotopic ossification in soft tissues such as thoracic muscles. Once the chest muscles are calcified, patients experience difficulty in inflating their lungs and may die from the resulting complications. The application of etidronate appeared to control the patient's ectopic bone formation (Bassett et al. 1969).

Later, BP compounds became commercially available and were used for treating Paget's





**Fig. 5.3** Pharmacological effect of nitrogen-containing BP on osteoclasts. Osteoclasts maintain their viability through cholesterol prenylation of membrane-bound G proteins (*above*). Osteoclasts internalize BP through bone resorption and are thought to lose their viability due to the blocked mevalonate pathway by BP. BP presents a

structural similarity to isopentenyl pyrophosphate (IPP) and can occupy farnesyl pyrophosphate synthase. As the result, the conversion from IPP to farnesyl pyrophosphate (FPP) is prevented (*bottom*). The lack of FPP significantly reduces GTPase prenylation and leads to premature termination of osteoclastic activities and cell death

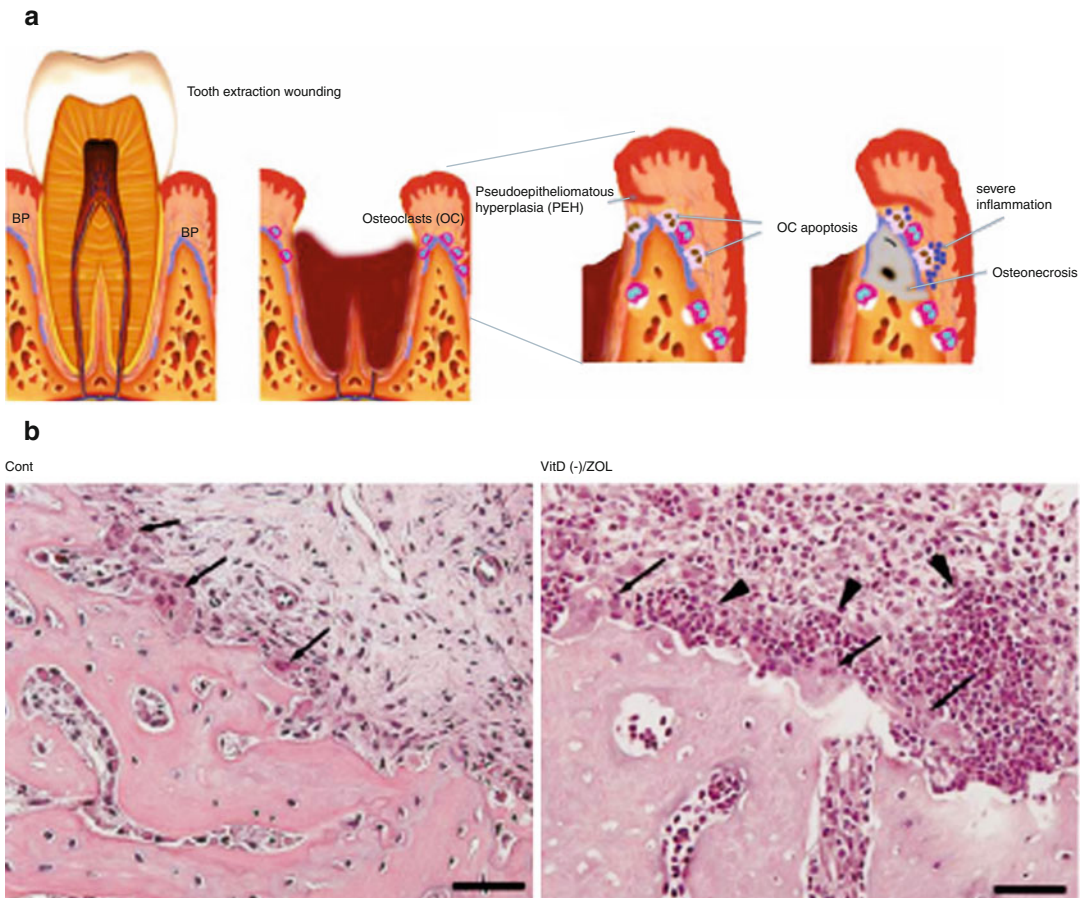
disease (Altman et al. 1973) and osteoporosis (Harris et al. 1999). Daily or weekly oral administration of BP was well accepted. However, due to side effects affecting the esophagus, intravenous infusions of BP have become available. While different BP compounds were generated to treat these metabolic bone diseases, nitrogen-containing BPs were found to be far more effective in decreasing bone resorption. They also controlled hypercalcemia caused by bone-residing or metastasizing tumors such as multiple myeloma and breast cancer. For these patient groups, high doses of BP are administered by intravenous infusion.

Bisphosphonates are released when bone is resorbed, but the released BP subsequently decreases the osteoclastic activity leading to a decrease in bone resorption (Fig. 5.3). The molecular structure of nitrogen-containing BPs was found to be very similar with an endogenous compound, isopentenyl pyrophosphate (IPP). IPP is a metabolite in the mevalonate pathway synthesizing cholesterol in the cell. In order to maintain cellular functions and viability, IPP needs to be converted to farnesyl pyrophosphate (FPP) by FPP synthase. After BP is internalized in the cell, BP can inhibit FPP synthase due to its molecular similarity to IPP and effectively

prevent the FPP synthesis. It has been demonstrated that FPP plays an essential role in functionalizing small GTPases by adding the lipid to these proteins. This process is called prenylation, by which small GTPases now become able to integrate in the cell membrane. These activated GTPases in the cell membrane are critical in organizing the actin ring of osteoclasts, allowing them to adhere to the bone surface and further develop the specific osteoclast morphology called the “ruffled border.” The lack of FPP results in the inadequate development of the osteoclastic cell morphology, leading to premature dehiscence as well as apoptosis (programmed cell death) (Itzstein et al. 2011; Li et al. 2011).

## 5.2 Osteonecrosis of the Jaw (ONJ)

Remarkably, clinical trials of BPs in patients with breast cancer metastatic to bone and in patients with multiple myeloma indicated the beneficial effect on hypercalcemia, without causing immediate, serious side effects (Body et al. 1999). In 2003, however, an unusual oral condition became evident where necrotic bone was exposed for longer than 8 weeks among patients who were treated with BPs (Marx 2003; Ruggiero et al.



**Fig. 5.4** (a) Hypothetical diagram of the pathological mechanism of osteonecrosis of the jaw (ONJ) following tooth extraction. (b) Osteoclasts (*arrows*) recruited as part of tooth extraction wound healing of rat alveolar bone (cont). In ONJ created by vitamin D deficiency and intra-

venous injection of zoledronate (VitD(-)/ZOL), osteoclasts (*arrows*) were surrounded by a cluster of neutrophils and lymphocytes (*arrowheads*) (From Hokugo et al. (2010))

2004). This condition is called osteonecrosis of the jaw (ONJ).

The majority of ONJ cases were reported as a complication of tooth extraction procedures, which increased the odds of developing ONJ by 16 times (Kyrgidis et al. 2008). If possible, medical practitioners should consider referring patients for dental treatment so that tooth extractions can be undertaken prior to prescribing intravenous BP therapy (Weitzman et al. 2007). In those situations where tooth extraction is required, antibiotic prophylaxis has prevented ONJ (Montefusco et al. 2008).

Tooth extraction is known to induce transient but robust osteoclastogenesis at the periphery of

the extraction socket (Fig. 5.4a). In normal wound healing following tooth extraction, the active osteoclastic bone resorption reduces the sharp edge of the socket and eventually forms a saddle shape residual ridge. It is highly conceivable that BP adsorbed onto the alveolar bone affects the viability of osteoclasts. Hokugo et al. (2010) generated the rat model of ONJ and reported that the prevalence of ONJ was positively associated with the abnormally increased number of osteoclasts in the tooth extraction area (Hokugo et al. 2010). Furthermore, during the early stages of ONJ pathogenesis, it was found that a cluster of inflammatory cells such as neutrophils and lymphocytes gathered around the osteoclasts on the

surface of the alveolar bone (Fig. 5.4b). This unusual observation may suggest that the BP-affected osteoclasts could recruit the inflammatory/immune cells in the oral mucosa through yet unknown signaling mechanisms, and the activated inflammatory/immune cells then induce the cytotoxic effect to alveolar bone resulting in osteonecrosis.

Because ONJ biopsy specimens that had been exposed to the oral cavity consistently show bacterial infection, it has been proposed that the pathological development of ONJ may be initiated by infectious agents (Mawardi et al. 2011). However, spontaneous development of ONJ has been reported particularly at the palatal torus and mandibular posterior plate areas, where the bone exposure appears to be secondary to the osteonecrosis. Furthermore, removable dentures were found to increase the odds of developing ONJ without the primary bacterial infection (Kyrgidis et al. 2008). It is well established that extensive denture wearing results in the loss of residual ridge alveolar bone, which is caused by osteoclastic bone resorption. Therefore, while the necrotic bone exposure invites opportunistic infection, which should require treatment, the common phenomenon among these susceptible conditions may lie in the increased osteoclastogenesis, which may play a key role in the development of ONJ. Although still speculative, the BP-affected osteoclasts may abnormally activate the oral mucosa immunity, which then induces cytotoxic overreaction, leading to osteonecrosis and/or oral epithelial ulceration. The more powerful intravenous BPs such as zoledronate are mainly responsible for the vast majority of ONJ cases reported, 88 % in one review (Filleul et al. 2010).

While the adverse effects of zoledronate can be devastating, other beneficial antitumor effects in breast and prostate cancer cells in culture have been demonstrated. Zoledronate can inhibit bony metastasis in highly tumorigenic cell lines by reducing cell proliferation and increasing cell death (Almubarak et al. 2011).

An alternative hypothesis for the pathogenesis of ONJ proposed that inflammation and microcalcification of small blood vessels were responsible for the mucosal soft tissue ischemia

(Meiller et al. 2012). In this theory, inflammation causes an acidic environment which would cause further release of calcium from its bound state with BP. This released calcium would induce more ischemia and mucosal ulceration, and a vicious circle ensues. This hypothesis would explain the difficulty in treating these lesions, but no new therapies are anticipated. Other theories have proposed that the primary effect of a potent BP is to cause premature senescence of oral mucosal cells (Kim et al. 2011b), thereby preventing wound closure following trauma.

The role of inflammation in the etiology of ONJ is unclear; however, severe periodontitis has been described as a risk factor (Yamazaki et al. 2012). Other studies have contrasted ONJ with other conditions that cause necrotic bone, such as suppurative osteomyelitis, and have described ONJ as having no inflammatory etiology but with drug toxicity as the main causative agent affecting normal bone turnover (Marx et al. 2012). Severe ONJ has been induced in rats given a potent BP (zoledronic acid), in the region where periodontitis had been induced with a ligature (Aghaloo et al. 2011). This would indicate that inflammation was a potent cofactor in the pathogenesis of ONJ. The features of this animal model included sequestration of necrotic alveolar bone in the inflamed region where plaque had accumulated around the ligature and extensive periosteal alveolar bone formation. These histological features are typically seen in ONJ-affected patients (Bedogni et al. 2008). Also, bone formation has been shown not to be affected in alendronate-treated rats (Kim et al. 2011a). It is unclear if ONJ could be completely prevented from occurring if oral hygiene was optimal.

The challenge is to identify those patients who have an early or subclinical bisphosphonate-associated ONJ rather than when necrotic bone becomes evident in the mouth. Before ONJ becomes evident, a 2–3-year symptom-free period is usually seen after treatment begins with high doses of BP. In one study of 24 patients, most of whom were treated with intravenous BP for malignancy, the mean length of time between starting treatment with BP and the development of clinical symptoms of ONJ was 31.8 months

(Abu-Id et al. 2008). Other studies have shown similar lag times, e.g., (Kos et al. 2010), but the delay cannot be related to the toxicity of the BP used as trauma is a major factor in the clinical onset of ONJ. A subclinical ONJ may not be evident on an X-ray because a bone loss of about 30–50 % is necessary before it becomes radiographically detectable. The ONJ lesion can be lytic, sclerotic, or a mixture of both (Morag et al. 2009). Cone beam CT can detect increases in cortical thickness, but because the changes are nonspecific, it is not yet known whether the excellent 3-D image quality is useful in early diagnosis. Magnetic resonance imaging, combined with contrast agents, may provide a useful imaging modality for early diagnosis (Khosla et al. 2007), but its main use may be in assessing the extent of BP-induced disease (Garcia-Ferrer et al. 2008).

Zoledronic acid has been shown to have in vivo antiangiogenic properties by reducing vascular endothelial growth factor (VEGF) (Vincenzi et al. 2005). Mucosa from patients with ONJ have been shown to produce less VEGF than mucosa from patients with no necrosis (Mozzati et al. 2012), which would reduce the ability of the mucosa to heal following minor trauma. In this hypothesis, BP released from the underlying bone following minor trauma causes reduced VEGF production by the mucosa and new blood vessels are unable to form.

It is hoped that future research may produce a simple laboratory test, perhaps involving the non-invasive sampling of gingival crevicular fluid, which would allow the identification of ONJ before symptoms develop. The serum concentration of cross-linked C-terminal telopeptide of collagen type I has been recommended to assess the surgical risk in those taking BP, with values of less than 100 pg/mL, representing a high risk (Marx et al. 2007). However, patients who have developed BP-induced ONJ are found with normal values (Carini et al. 2012), (Conte-Neto et al. 2011). Bone turnover is suppressed in the majority of patients treated with BP (Eekman et al. 2011), but normal values of C-terminal telopeptide are seen in those with ONJ who continue receiving BP. For the individual patient, the C-terminal telopeptide test does not accurately

predict the development of ONJ (Kunchur et al. 2009).

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### 5.3 The Nonexposed Variant of Bisphosphonate-Induced ONJ

The American Association of Oral and Maxillofacial Surgeons has described the staging of bisphosphonate-induced ONJ and included a nonexposed variant. This stage is characterized by a lack of bone exposure but which may include a variety of nonspecific signs and symptoms such as alveolar bone expansion, dull jaw pain, and either bony sclerosis or osteolysis (Ruggiero et al. 2009). Osteosclerosis may be an important radiological sign as it was present consistently in clinically symptomatic areas of one third of these patients (Hutchinson et al. 2010). Other clinical symptoms associated with this condition include gingival swelling and a sinus tract, but their nonspecific nature makes it difficult to distinguish them from other dental infections. In a European study involving five centers, of those patients diagnosed with the nonexposed variant of ONJ, most (92 %) presented with jaw pain, about half (51 %) with a sinus tract, and about a third (36.4 %) with bone enlargement (Fedele et al. 2010).

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### 5.4 Implant Osseointegration in BP-Treated Patients

Surgical manipulation of alveolar bone will induce inflammation and bone remodeling. In this process, if excessive numbers of inflammatory cells are recruited in the jawbone of BP-treated patients, there may be an increased chance of developing ONJ. There has been an intensive debate over whether surgical procedures involving osteotomy and implant fixture placement could also result in ONJ. Patients taking oral BP for longer than 3 years are at an increased risk of ONJ, especially if corticosteroids are also taken concurrently. The American Association of Oral and Maxillofacial Surgeons has advised that oral BP be discontinued 3 months before and after

implant placement, if planned in consultation with the patient's physician (Ruggiero et al. 2009). However, these practical guidelines are empirical and lacking high-quality evidence.

There is a clear trend that 1–10 % of cancer patients with intravenous infusion of high-dose BPs might experience ONJ (Reid and Cornish 2011). The intravenous infusion of high doses of BP presents a significant risk for ONJ, and thus patients receiving this treatment may not be suitable for surgical implant placement. On the contrary, osteoporosis patients taking oral BPs develop a much lower ONJ prevalence (Solomon et al. 2012). However, the number of osteoporotic patients with alendronate alone exceeds 20 million in the USA, and thus they are more relevant to routine dental treatment, including implant therapy.

Jeffcoat (2006) reported a single-blind controlled study involving 50 postmenopausal osteoporotic female patients with a total of 210 implants (Jeffcoat 2006). One half of the patients received oral BP treatment. Following implant placement, all patients were followed for 3 years or longer. None of the 102 implants in the BP patients were lost, whereas the success rate of the control patient group was 99.2 %. ONJ was not reported during this study.

A short-term follow-up study of 61 female patients receiving oral BPs was reported (Fugazzotto et al. 2007). One hundred and sixty-nine implants were placed in these patients either immediately after tooth extraction or in the edentulous area. At the 12- to 24-month follow-up examination, all implants were present and restored with appropriate prostheses. This study also reported that one patient exhibited 2×3-mm bone exposure in a mandibular torus adjacent to the first molar extraction site. The exposed bone was noticed at the 1-week post extraction examination and was debrided, and the implant placement took place 4 weeks later without any further complications. The ONJ prevalence in this report was therefore 1.6 %; however, no implant loss was experienced.

A direct mail survey was undertaken of 1,319 female patients over the age of 40, who had surgical implant placement (Grant et al. 2008). Out of

458 responses, 343 patients did not take oral BPs, whereas 115 patients reported the use of oral BP. Of these 115 patients, 89 patients reported the use of oral BP before implant surgery, and 26 patients started oral BP treatment after implant surgery. None of the patients responding to the survey reported symptoms related to ONJ. Two of the 86 patients experienced an episode of implant loss before osseointegration. Both of the failed implants were placed in the posterior region. However, the incidence of unsuccessful osseointegration in oral BP-treated patients appears to be within the normal range and similar to that of untreated patients.

A retrospective chart review was reported (Koka et al. 2010). Three hundred and seventy postmenopausal female patients received implant placement, and 69 patients listed oral BP as one of their medications. The subsequent telephone interview obtained the answers to the questionnaire from 55 patients with oral BP treatment and found that 1 out of 121 implants was lost.

These reports suggest that oral BP treatment does not influence implant osseointegration per se. Furthermore, the failed implants in patients treated with oral BP were not due to the development of ONJ. As such, the American Dental Association (ADA) issued a position paper in 2008 stating that oral BP treatment would not contraindicate dental implant treatment (Edwards et al. 2008).

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## 5.5 Implant Failure in Patients Treated with BPs

Despite the assurance from ADA supported by the published reports, implant failures in those treated with BP continue to appear in the literature (Tables 5.1 and 5.2). The following are some of the highlights.

### 5.5.1 En Bloc Alveolar Bone Necrosis with Osseointegrated Implant

The number of adverse events following low-dose exposure of BP is low (Watts and Diab



**Table 5.1** Case reports in patients treated with BPs exhibiting implant failure prior to loading

| Patient |     | Implant                               |                                                                                                                               |                 |                            | Symptom                                                                                                                                                | BP                       |       |
|---------|-----|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-----------------|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|-------|
| Age     | Sex | Location                              | Surgery                                                                                                                       | BP drug holiday | Service                    |                                                                                                                                                        | BP                       | Route |
| 63      | M   | #4, #12                               | One stage                                                                                                                     | None reported   | None specified: No loading | Pain (#12) after implantation; probing depth 12 mm (#4)                                                                                                | Alendronate              | Oral  |
| 65      | F   | #18, #19, #20, #29, #30               | Prophylactic antibiotics, acetaminophen, ibuprofen as needed                                                                  | None reported   | 6 weeks post implantation  | Fluctuant swelling, radiolucency and large bone resorption (#9, #20): after the corrective surgery, necrotic bone exfoliated but otherwise no symptoms | Alendronate              | Oral  |
| 62      | F   | #2, #3, #4, #6, #8, #9, #11, #13, #15 | #2, #8, #9, #10, #11 extraction and socket preservation with freeze-dried bone; and sinus grafting prior to implant placement | None reported   | 2 month post implantation  | Necrotic bone exfoliation at #11, #13, #15; bone defect at sinus floor; sinusitis                                                                      | Risedronate (35 mg/week) | Oral  |
| 68      | F   | #21, #19, #18                         | None specified                                                                                                                | None reported   | 1 year; 4 years            | Pain, gingival bleeding 1 year after implant placement/ #9: gingival swelling, bleeding, radiolucency 4 year after implant placement                   | Alendronate              | Oral  |
| 65      | F   | #30, #31?                             | None specified                                                                                                                | 3 months        | 4 months                   | Oral mucosa breakdown, purulent discharge, periapical radiolucency                                                                                     | Clodronate               | IV    |

2010). Adverse events are more common when patients have received higher doses of BP. In a case report, a 54-year-old woman had been treated with an intravenous infusion of BP for breast cancer bone metastases for 2 years and developed ONJ (Shirota et al. 2009). The patient complained of severe pain and ulceration at the maxillary left molar area, where two implants had been functioning satisfactorily for 6 years.

The clinical presentation was consistent with ONJ, and the affected maxillary alveolar bone containing two implants was surgically sequestered (Fig. 5.5a). The implant surface was exposed on the buccal area. Histological evaluation revealed the en bloc alveolar bone was largely non-vital with empty osteocytic lacunae. However, the remaining bone-to-implant contact appeared to be maintained (Fig. 5.5b, c). It is



| Duration                     | Primary diagnosis                                                                   | Biopsy                                                                          | Treatment                                                                                                            | Reference                     |
|------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|-------------------------------|
| >10 years?                   | Osteoporosis, erosive osteoarthritis, history of wrist and thoracic spine fractures | None reported                                                                   | #12 removed in 4 days; #4 removed in 3 weeks followed by teriparatide 20 µg SQ                                       | Narongroeknawin et al. (2010) |
| >10 years                    | Osteoporosis, arthritis, history of hip fracture                                    | None reported                                                                   | Drainage, antibiotics, CHX followed by open degranulation, human mineralized cancellous bone graft with tetracycline | Wang et al. (2007)            |
| 4 years                      | Osteoporosis                                                                        | Biopsy, osteonecrosis, and chronically inflamed granulation tissue              | Antibiotics, necrotic bone removal; open sinus exploration; #15 explantation                                         | Brooks et al. (2007)          |
| 2 years at implant placement | Osteoporosis, rheumatoid arthritis                                                  | Biopsy, acute and chronic non-specific inflammation with necrotic bone fragment | Discontinuation of alendronate, curettage, antibiotics, CHX                                                          | Park et al. (2010)            |
| 5 years                      | Multiple myeloma                                                                    | Biopsy, implant showed osseointegration                                         | En-block resection of alveolar bone with 2 implants                                                                  | Favia et al. (2011)           |

unclear if the osseointegrated bone in this patient was still vital and actively remodeled.

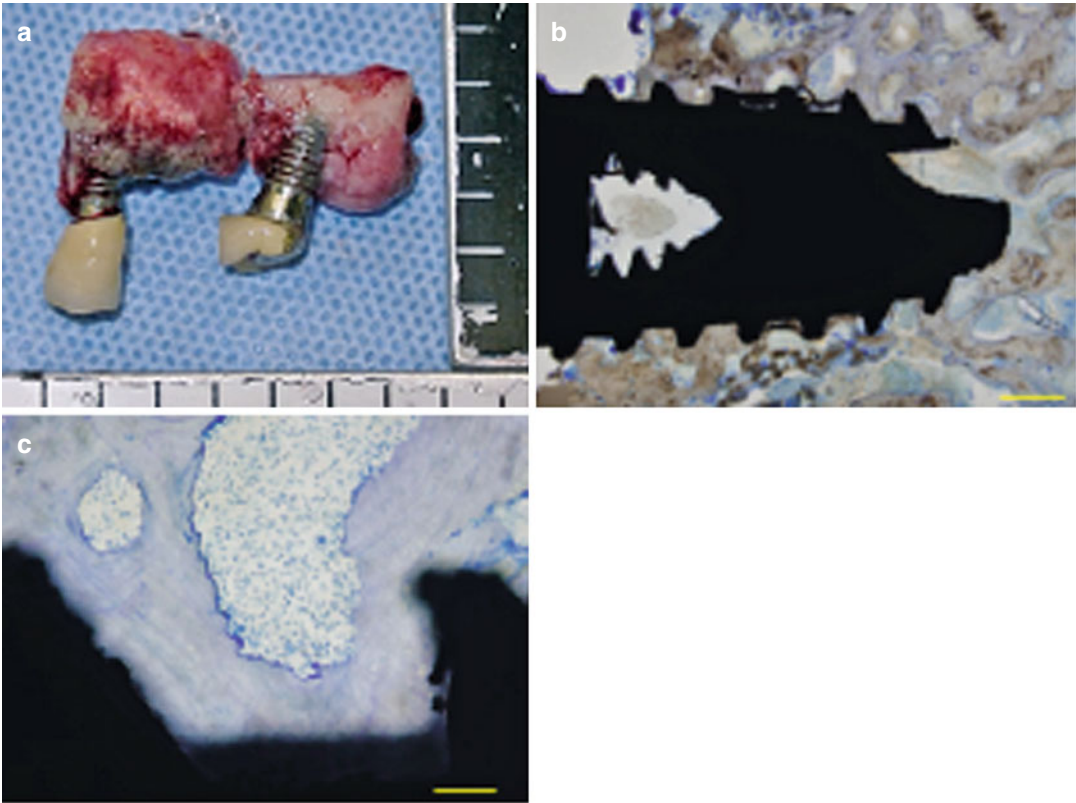
A similar report of a 65-year-old woman treated with an intravenous BP infusion was described (Favia et al. 2011). Four months after implant placement in the mandibular molar area, ONJ-like symptoms occurred in alveolar bone surrounding the implant. Histological evaluation of the en bloc sequestration indicated

osseointegration particularly at the apex of the inserted implant.

More recently, an ONJ-like lesion was reported in a 69-year-old man in the region of two dental implants placed in the mandibular left molar region 10 years previously (Yuan et al. 2012). The patient had developed osteoporosis and had been treated with oral BPs for 3 years. One of the implants was removed as part of the

**Table 5.2** Case reports in patients treated with BPs exhibiting implant failure after loading

| Patient |     | Implant                   |                                              |                                  |                                       | Symptom                                                         |
|---------|-----|---------------------------|----------------------------------------------|----------------------------------|---------------------------------------|-----------------------------------------------------------------|
| Age     | Sex | Location                  | Surgery                                      | BP drug holiday                  | Service                               |                                                                 |
| 67      | F   | #3, #4                    | None specified                               | None (5 mosince initial symptom) | 1 year                                | Swelling, redness, pain, bone exposure, fixture threads exposed |
| 63      | F   | #19, #21                  | #21 immediate implant placement with Bio-Oss | None reported                    | 3 year                                | Swelling, pain bone exposure                                    |
| 64      | F   | #2, #3, #5, #12, #14, #15 | None specified                               | None reported                    | 4 year                                | Radiolucency surrounding implants without clinical symptoms     |
| 54      | F   | #14, #16                  | None specified                               | None reported                    | None specified but served for loading | Pain, bone exposure                                             |
| 69      | M   | #8, #19                   | None specified                               | None reported                    | 10 years                              | Swelling, pain radiolucency, 9 mm probing depth                 |



**Fig. 5.5** (a) The resected specimen from a 54-year-old female patient who began intravenous BP infusion 4 years after implant placement. (b) Histological evaluation of the biopsy specimen showed that most of the implant surface

was in direct contact with bone. (c) Bone-to-implant contact indicated the maintained osseointegration, while the alveolar bone appeared to be devitalized (From Shirota et al. (2009))

| BP                       |       |          | Primary diagnosis | Biopsy                                  | Treatment                                                | Reference             |
|--------------------------|-------|----------|-------------------|-----------------------------------------|----------------------------------------------------------|-----------------------|
| BP                       | Route | Duration |                   |                                         |                                                          |                       |
| Alendronate (70 mg/week) | Oral  | 1 year   | Osteoporosis      | None reported                           | Antibiotics, CHX, explantation                           | Shin et al. (2010)    |
| Alendronate (70 mg/week) | Oral  | 6 year   | Osteoporosis      | None reported                           | Antibiotics                                              | Bedogni et al. (2010) |
| Risedronate (35 mg/week) | Oral  | 13 year  | Paget's disease   | None reported                           | None                                                     | Torres et al. (2008)  |
| None specified           | IV    | 2 year   | Breast cancer     | Biopsy, implant showed osseointegration | Sequestrectomy of left maxilla; antibiotics, HBO         | Shirota et al. (2009) |
| Risedronate              | Oral  | 2 year   | Osteoporosis      | Biopsy, implant showed osseointegration | Antibiotics, open debridement surgery, CHX, explantation | Yuan et al. (2012)    |
| Alendronate              | Oral  | 1 year   |                   |                                         |                                                          |                       |

sequestrectomy. Histological evaluation indicated that the implant had maintained osseointegration, but that the surrounding alveolar bone was necrotic with empty bone marrow spaces.

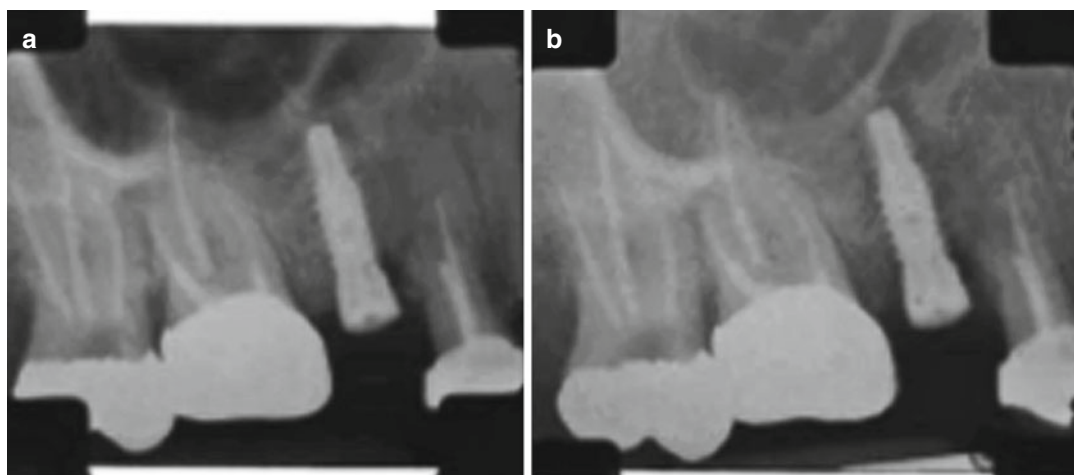
A common observation of these cases is the maintained close association between bone and the implant surface, despite the surrounding necrotic alveolar bone. Two cases started the BP treatment long after implant placement, suggesting that the development of ONJ was not activated by the implant surgery. However, after BP treatment started, the alveolar bone containing the osseointegrated implants developed ONJ, indicating some factors associated with implant maintenance might have triggered the pathogenesis of this lesion. It is advised that patients with implants should be regularly reviewed when they start BP treatments.

### 5.5.2 Failure of Implant Osseointegration

A 63-year-old man with osteoporosis and receiving oral BP therapy for 5 years experienced pain at one of the implant sites (Narongroeknawin et al. 2010). He had received two implants in the right

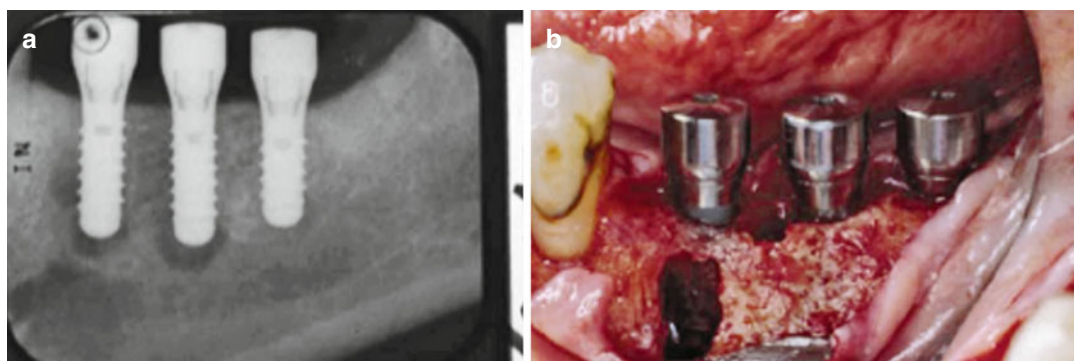
and left maxillary premolar region. The painful implant was removed 4 days after implant placement surgery, but the explantation site did not heal for 1 month, and the surrounding tissue showed inflammation. The remaining implant was asymptomatic; however, the probing depth reached 12 mm and the periapical radiograph indicated bone loss around the implant (Fig. 5.6). The clinical presentation indicated the lack of osseointegration, and the implant was also removed. In addition to the radiological finding of a “funnel-like” bone resorption around the implant, it was reported that the buccal cortical bone was missing.

A 65-year-old woman with osteoporosis and oral BP treatment received five oral implants in the mandibular posterior edentulous areas (Wang et al. 2007). However, 6 weeks after implant placement, the left mandibular molar region exhibited swelling and suppuration. The periapical radiograph revealed radiolucencies around the implants (Fig. 5.7). There was a “funnel”-type bone resorption surrounding the affected implants. Treatment included removing the granulation tissue with open curettage followed by placement of a human mineralized cancellous bone graft with tetracycline. It was reported that these implants survived.



**Fig. 5.6** (a) Periapical radiograph depicting an implant placed in the maxillary premolar area. (b) The funnel-like bone resorption around the implant developed, and the

implant was removed 3 weeks later (From Narongroeknawin et al. (2010))



**Fig. 5.7** (a) Six weeks postoperative. Radiograph showed radiolucency at the apex of and surrounding the implant fixtures. (b) Open curettage surgery identified the exten-

sive bone resorption and granulosomatous tissue formation around the implants (From Wang et al. (2007))

In another case report, a 69-year-old woman with osteoporosis, who was treated with oral BP, developed pain and discomfort after multiple implants were surgically placed in the mandibular molar area (Park et al. 2010). A radiolucency was noted around the implant. The biopsy revealed acute and chronic nonspecific inflammation with granulation tissue formation and a necrotic bone fragment.

In these case reports of osteoporotic patients receiving long-term BP, a funnel-like bone resorption developed around multiple implants. This is surprising given the marked long-term effect of BP in reducing osteoclastic activity.

These patients exhibited an extensive bone resorption, and a granulosomatous tissue was formed around the implant surface. These cases represent an unfavorable response to the surgical placement of implants, resulting in the failure of osseointegration. In a case report, a 62-year-old woman, who had osteoporosis treated with oral BP treatment for 4 years, developed ONJ in the area of the maxillary molar region 2 months after implant placement (Brooks et al. 2007). The open sinus exploration identified necrotic bone sequestration, and histological evaluation reported chronically inflamed granulation tissue. However, it is unclear if the long-term BP treatment could

cause the unusual chronic inflammatory reaction in the implant osteotomy bed.

### 5.5.3 Osteonecrosis Following Implant Placement

In a case report, ONJ was expressed as the exposure of necrotic bone around implants in a 67-year-old woman with osteoporosis who had only received oral BP for 1 year (Shin et al. 2010). The BP treatment had started at about the same time as the implant placement. The implants showed mobility, percussion sensitivity, and 10-mm probing depth. Surgical exploration revealed the exposed implant buccal surface with necrotic bony sequestrations; however, no significant inflammatory granulation tissue was observed. Both implants were removed with debridement of the associated necrotic bone.

Some case reports describe successful dental implant placement with extensive bone grafting procedures, despite severe osteoporosis and treatment with BP. Bone regeneration was described in such a 64-year-old patient receiving multiple implants in the maxillary molar regions (Torres et al. 2008). The authors had used platelet-rich plasma as part of the bone augmentation, and they recommended it as providing beneficial angiogenic properties in these patients. The initial healing took place uneventfully, and all implants were loaded 4 months after the surgery. The patient was free from any pain and discomfort. Three years after the implant treatment, the implant-supported prosthesis was still in function, and no significant inflammation was reported.

Other case reports document implant osseointegration followed by ONJ in patients taking oral BP. A 63-year-old woman with osteoporosis had been treated with oral BP for 6 years and had received two mandibular molar implants (Bedogni et al. 2010). The surgical healing was uneventful and both implants were loaded 6 months later. After 2 years of implant placement, the patient came back with complaints of mandibular pain and swelling. Several courses of antibiotic treatments did not improve the condition. A panoramic radiograph and CT scan

revealed an increased bone marrow density with peri-implant sequestration. The patient was diagnosed with ONJ.

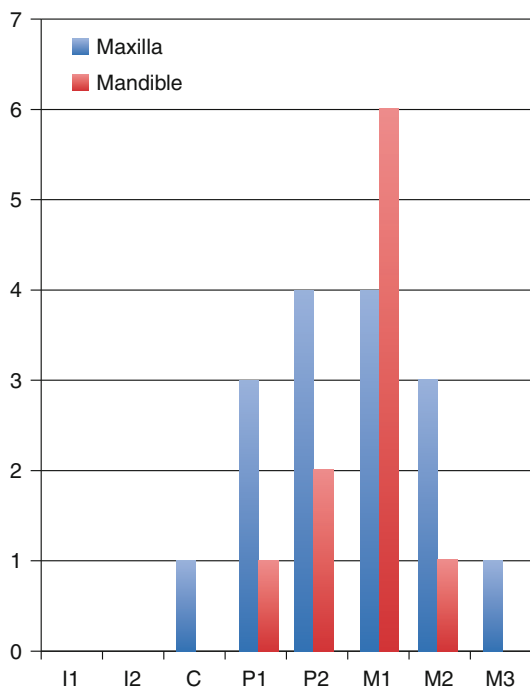
These cases demonstrate an uneventful course of implant surgery with wound healing. All implants were loaded and the implants then appeared to become separated from the surrounding bone. Clinical presentations vary and are likely to be dependent on the presence of a superimposed infection and/or an inflammatory reaction. In other words, the possible lesions can be asymptomatic until infection and inflammation intervene and cause pain and discomfort. Therefore, it is not certain when the pathology had begun as the quiescent bone pathology around the implant might have existed for an extended period.

Although generalization cannot be made from these case reports, implant-related complications in BP-treated patients appear to occur more frequently in the posterior areas of the maxilla and the mandible (Fig. 5.8). The most frequently affected site was the region of the mandibular first molar. This has also been noted in other studies with the ONJ incidence affecting the mandible twice as often as the maxilla (Ficarra and Beninati 2007).

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## 5.6 Future Perspectives and Conclusions

A recent case-control study involved 337 middle-aged women who had 1,181 implants placed over 7-year period. It evaluated those women with one or more implant failures (Yip et al. 2012). The odds of oral BP use was 2.69 times higher in women for whom implants failed. Contrary to the previous studies, this study indicated a possible link between oral BP and implant failure. This study restricted the selection of patient data between 1997 and 2004 because after the first report on ONJ in 2003, the implant practice for BP users might have changed, which was thought to confound the data evaluation. Furthermore, 114 cases of implant failure were identified, whereas there were 223 controls. BP use was significantly higher in the case group (9.65 %) than in the control group (4.04 %;  $p=0.04$ ). Another significant difference was the number of



**Fig. 5.8** Distribution of implant-related incidences in BP-treated patients

implants placed; the case group received a mean of 4.30 (sd=2.97), whereas the control group received a mean of 3.10 (sd=2.19;  $p=0.02$ ).

A preliminary retrospective chart review at the University of California, Los Angeles (UCLA) Implant Center revealed a 95 % success rate of implants placed in BP-treated patients. However, the percentage of BP-treated patients that experienced implant failure was 14.8 %. Multiple implants tend to fail in certain patients, which have been described as an “implant cluster failure” (see Chap. 4). The clustered nature of implant failure has suggested that the involvement of patients’ genetic and/or environmental factors contributes to the loss of osseointegration. The lack of a clustering tendency in implant failure experienced by BP-treated patients may indicate that other critical factors may be more influential. It is conceivable that because the BP adsorption pattern is not uniform within the alveolar bone, the effect of BPs may vary for each implant placed in different sites of the same patient.

To date, the pathological etiology of ONJ has not been established. The evaluation strategies of implant success and failure for those patients

who have been treated with BPs may require careful consideration. The available evidence does not point to the role of orally administered BPs for osteoporosis patients in the unexplained failure of implants. However, individual cases with BP-treated patients, who experienced rather catastrophic implant failure, have emerged (Tables 5.1 and 5.2). After implant placement, a strict follow-up procedure should be established for BP-treated patients.

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## References

- Abu-Id MH, Warnke PH, Gottschalk J, Springer I, Wiltfang J, Acil Y et al (2008) ‘Bis-phossy jaws’ – high and low risk factors for bisphosphonate-induced osteonecrosis of the jaw. *J Craniomaxillofac Surg* 36(2):95–103
- Aghaloo TL, Kang B, Sung EC, Shoff M, Ronconi M, Gotcher JE et al (2011) Periodontal disease and bisphosphonates induce osteonecrosis of the jaws in the rat. *J Bone Miner Res* 26(8):1871–1882
- Almubarak H, Jones A, Chaisuparat R, Zhang M, Meiller TF, Scheper MA (2011) Zoledronic acid directly suppresses cell proliferation and induces apoptosis in highly tumorigenic prostate and breast cancers. *J Carcinog* 10:2
- Altman RD, Johnston CC, Khairi MR, Wellman H, Serafini AN, Sankey RR (1973) Influence of disodium etidronate on clinical and laboratory manifestations of Paget’s disease of bone (osteitis deformans). *N Eng J Med* 289(26):1379–1384
- Bassett CA, Donath A, Macagno F, Preisig R, Fleisch H, Francis MD (1969) Diphosphonates in the treatment of myositis ossificans. *Lancet* 2(7625):845
- Bedogni A, Blandamura S, Lokmic Z, Palumbo C, Ragazzo M, Ferrari F et al (2008) Bisphosphonate-associated jawbone osteonecrosis: a correlation between imaging techniques and histopathology. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 105(3):358–364
- Bedogni A, Bettini G, Totola A, Saia G, Nocini PF (2010) Oral bisphosphonate-associated osteonecrosis of the jaw after implant surgery: a case report and literature review. *J Oral Maxillofac Surg* 68(7):1662–1666
- Body JJ, Lortholary A, Romieu G, Vigeneron AM, Ford J (1999) A dose-finding study of zoledronate in hypercalcemic cancer patients. *J Bone Min Res* 14(9):1557–1561



- Briner WW, Francis MD (1973) In vitro and in vivo evaluation of anti-calculus agents. *Calcif Tissue Res* 11(1):10–22
- Brooks JK, Gilson AJ, Sindler AJ, Ashman SG, Schwartz KG, Nikitakis NG (2007) Osteonecrosis of the jaws associated with use of Risedronate: report of 2 new cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 103(6):780–786
- Carini F, Saggese V, Porcaro G, Barbano L, Baldoni M (2012) Surgical protocol in patients at risk for bisphosphonate osteonecrosis of the jaws: clinical use of serum telopeptide CTX in preventive monitoring of surgical risk. *Ann Stomatol (Roma)* 3(1):31–36
- Conte-Neto N, Bastos AS, Spolidorio LC, Marcantonio RA, Marcantonio E Jr (2011) Oral bisphosphonate-related osteonecrosis of the jaws in rheumatoid arthritis patients: a critical discussion and two case reports. *Head Face Med* 7:7 DOI: [10.1186/1746-160X-7-7](https://doi.org/10.1186/1746-160X-7-7)
- Edwards BJ, Hellstein JW, Jacobsen PL, Kaltman S, Mariotti A, Migliorati CA (2008) Updated recommendations for managing the care of patients receiving oral bisphosphonate therapy: an advisory statement from the American Dental Association Council on Scientific Affairs. *J Am Dent Assoc* 139(12):1674–1677
- Eekman DA, Bultink IE, Heijboer AC, Dijkman BA, Lems WF (2011) Bone turnover is adequately suppressed in osteoporotic patients treated with bisphosphonates in daily practice. *BMC Musculoskelet Disord* 12:167 DOI:[10.1186/1471-2474-12-167](https://doi.org/10.1186/1471-2474-12-167)
- Favia G, Piattelli A, Sportelli P, Capodiferro S, Iezzi G (2011) Osteonecrosis of the posterior mandible after implant insertion: a clinical and histological case report. *Clin Implant Dent Relat Res* 13(1):58–63
- Fedele S, Porter SR, D'Aiuto F, Aljohani S, Vescovi P, Manfredi M et al (2010) Nonexposed variant of bisphosphonate-associated osteonecrosis of the jaw: a case series. *Am J Med* 123(11):1060–1064
- Ficarra G, Beninati F (2007) Bisphosphonate-related osteonecrosis of the jaws: an update on clinical, pathological and management aspects. *Head Neck Pathol* 1(2):132–140
- Filleul O, Crompton E, Saussez S (2010) Bisphosphonate-induced osteonecrosis of the jaw: a review of 2,400 patient cases. *J Cancer Res Clin Oncol* 136(8):1117–1124
- Francis MD, Valent DJ (2007) Historical perspectives on the clinical development of bisphosphonates in the treatment of bone diseases. *J Musculoskelet Neuronal Interact* 7(1):2–8
- Fugazzotto PA, Lightfoot WS, Jaffin R, Kumar A (2007) Implant placement with or without simultaneous tooth extraction in patients taking oral bisphosphonates: postoperative healing, early follow-up, and the incidence of complications in two private practices. *J Periodontol* 78(9):1664–1669
- Garcia-Ferrer L, Bagan JV, Martinez-Sanjuan V, Hernandez-Bazan S, Garcia R, Jimenez-Soriano Y et al (2008) MRI of mandibular osteonecrosis secondary to bisphosphonates. *AJR Am J Roentgenol* 190(4):949–955
- Grant BT, Amenado C, Freeman K, Kraut RA (2008) Outcomes of placing dental implants in patients taking oral bisphosphonates: a review of 115 cases. *J Oral Maxillofac Surg* 66(2):223–230
- Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M et al (1999) Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA* 282(14):1344–1352
- Hokugo A, Christensen R, Chung EM, Sung EC, Felsenfeld AL, Sayre JW et al (2010) Increased prevalence of bisphosphonate-related osteonecrosis of the jaw with vitamin D deficiency in rats. *J Bone Miner Res* 25(6):1337–1349
- Hutchinson M, O'Ryan F, Chavez V, Lathon PV, Sanchez G, Hatcher DC et al (2010) Radiographic findings in bisphosphonate-treated patients with stage 0 disease in the absence of bone exposure. *J Oral Maxillofac Surg* 68(9):2232–2240
- Itzstein C, Coxon FP, Rogers MJ (2011) The regulation of osteoclast function and bone resorption by small GTPases. *Small GTPases* 2(3):117–130
- Jeffcoat MK (2006) Safety of oral bisphosphonates: controlled studies on alveolar bone. *Int J Oral Maxillofac Implants* 21(3):349–353
- Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D et al (2007) Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 22(10):1479–1491
- Kim JH, Park YB, Li Z, Shim JS, Moon HS, Jung HS et al (2011a) Effect of alendronate on healing of extraction sockets and healing around implants. *Oral Dis* 17(7):705–711
- Kim RH, Lee RS, Williams D, Bae S, Woo J, Lieberman M et al (2011b) Bisphosphonates induce senescence in normal human oral keratinocytes. *J Dent Res* 90(6):810–816
- Koka S, Babu NM, Norell A (2010) Survival of dental implants in post-menopausal bisphosphonate users. *J Prosthodont Res* 54(3):108–111
- Kos M, Kuebler JF, Luczak K, Engelke W (2010) Bisphosphonate-related osteonecrosis of the jaws: a review of 34 cases and evaluation of risk. *J Craniomaxillofac Surg* 38(4):255–259
- Kunchur R, Need A, Hughes T, Goss A (2009) Clinical investigation of C-terminal cross-linking telopeptide test in prevention and management of bisphosphonate-associated osteonecrosis of the jaws. *J Oral Maxillofac Surg* 67(6):1167–1173
- Kyrgidis A, Vahtsevanos K, Koloutsos G, Andreadis C, Boukovinas I, Teleioudis Z et al (2008) Bisphosphonate-related osteonecrosis of the jaws: a case-control study of risk factors in breast cancer patients. *J Clin Oncol* 26(28):4634–4638
- Li B, Ling Chau JF, Wang X, Leong WF (2011) Bisphosphonates, specific inhibitors of osteoclast function and a class of drugs for osteoporosis therapy. *J Cell Biochem* 112(5):1229–1242

- Marx RE (2003) Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 61(9): 1115–1117
- Marx RE, Cillo JE Jr, Ulloa JJ (2007) Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment. *J Oral Maxillofac Surg* 65(12):2397–2410
- Marx RE, Sawatari Y, Fortin M, Broumand V (2012) Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg* 63(11):1567–1575
- Mawardi H, Giro G, Kajiya M, Ohta K, Almazrooa S, Alshwaimi E et al (2011) A role of oral bacteria in bisphosphonate-induced osteonecrosis of the jaw. *J Dent Res* 90(1339–45)
- Meiller T, Almubarak H, Weikel D, Brahim J, Scheper M (2012) Bisphosphonate-associated osteonecrosis of the jaw: are we dealing with a localized non-traditional calciphylaxis? *Open Dent J* 6:5–7
- Montefusco V, Gay F, Spina F, Miceli R, Maniezzo M, Teresa Ambrosini M et al (2008) Antibiotic prophylaxis before dental procedures may reduce the incidence of osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates. *Leuk Lymphoma* 49(11):2156–2162
- Morag Y, Morag-Hezroni M, Jamadar DA, Ward BB, Jacobson JA, Zwetchkenbaum SR et al (2009) Bisphosphonate-related osteonecrosis of the jaw: a pictorial review. *Radiographics* 29(7):1971–1984
- Mozzati M, Martinasso G, Maggiora M, Scoletta M, Zambelli M, Carossa S et al (2012) Oral mucosa produces cytokines and factors influencing osteoclast activity and endothelial cell proliferation, in patients with osteonecrosis of jaw after treatment with zoledronic acid. *Clin Oral Investig* Aug 3 [Epub ahead of print] DOI: [10.1007/s00784-012-0800-7](https://doi.org/10.1007/s00784-012-0800-7)
- Narongroeknawin P, Danila MI, Humphreys LGJ, Barasch A, Curtis JR (2010) Bisphosphonate-associated osteonecrosis of the jaw, with healing after teriparatide: a review of the literature and a case report. *Spec Care Dentist* 30(2):77–82
- Park W, Kim NK, Kim MY, Rhee YM, Kim HJ (2010) Osteonecrosis of the jaw induced by oral administration of bisphosphonates in Asian population: five cases. *Osteoporos Int* 21(3):527–533
- Reid IR, Cornish J (2011) Epidemiology and pathogenesis of osteonecrosis of the jaw. *Nat Rev Rheumatol* 29(8):2
- Roelofs AJ, Stewart CA, Sun S, Blazewska KM, Kashemirov BA, McKenna CE et al (2012) Influence of bone affinity on the skeletal distribution of fluorescently labeled bisphosphonates in vivo. *J Bone Miner Res* 27(4):835–847
- Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL (2004) Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 62(5):527–534
- Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B (2009) American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws—2009 update. *J Oral Maxillofac Surg* 67(5 Suppl): 2–12
- Shin EY, Kwon YH, Herr Y, Shin SI, Chung JH (2010) Implant failure associated with oral bisphosphonate-related osteonecrosis of the jaw. *J Periodontal Implant Sci* 40(2):90–95
- Shirota T, Nakamura A, Matsui Y, Hatori M, Nakamura M, Shintani S (2009) Bisphosphonate-related osteonecrosis of the jaw around dental implants in the maxilla: report of a case. *Clin Oral Implants Res* 20(12): 1402–1408
- Solomon DH, Mercer E, Woo SB, Avorn J, Schneeweiss S, Treister N (2012) Defining the epidemiology of bisphosphonate-associated osteonecrosis of the jaw: prior work and current challenges. *Osteoporos Int* Jun 16. [Epub ahead of print] DOI: [10.1007/s00198-012-2042-6](https://doi.org/10.1007/s00198-012-2042-6)
- Torres J, Tamimi F, Garcia I, Cebrian JL, Lopez-Cabarcos E, Lopez A (2008) Management of atrophic maxilla in severe osteoporosis treated with bisphosphonates: a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 106(5):668–672
- Vincenzi B, Santini D, Dicuonzo G, Battistoni F, Gavasci M, La Cesa A et al (2005) Zoledronic acid-related angiogenesis modifications and survival in advanced breast cancer patients. *J Interferon Cytokine Res* 25(3):144–151
- Wang HL, Weber D, McCauley LK (2007) Effect of long-term oral bisphosphonates on implant wound healing: literature review and a case report. *J Periodontol* 78(3):584–594
- Watts NB, Diab DL (2010) Long-term use of bisphosphonates in osteoporosis. *J Clin Endocrinol Metab* 95(4):1555–1565
- Weitzman R, Sauter N, Eriksen EF, Tarassoff PG, Lacerna LV, Dias R et al (2007) Critical review: updated recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in cancer patients—May 2006. *Crit Rev Oncol Hematol* 62(2):148–152
- Yamazaki T, Yamori M, Ishizaki T, Asai K, Goto K, Takahashi K, et al (2012) Increased incidence of osteonecrosis of the jaw after tooth extraction in patients treated with bisphosphonates: a cohort study. *Int J Oral Maxillofac Surg* 41(11):1397–403
- Yip JK, Borrell LN, Cho SC, Francisco H, Tarnow DP (2012) Association between oral bisphosphonate use and dental implant failure among middle-aged women. *J Clin Periodontol* 39(4):408–14
- Yuan K, Chen KC, Chan YJ, Tsai CC, Chen HH, Shih CC (2012) Dental implant failure associated with bacterial infection and long-term bisphosphonate usage: a case report. *Implant Dent* 21(1):3–7

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